# STUDY OF PREOPERATIVE CHEMOTHERAPY IN CERVICAL CANCERS STAGES IB2, IIA2 AND IIB

**DEPARTMENT OF SURGICAL ONCOLOGY**

**KILPAUK MEDICAL COLLEGE AND**

**GOVERNMENT ROYAPETTAH HOSPITAL**

**CHENNAI**

***Dissertation submitted in partial fulfillment of***

**MCH BRANCH VII (SURGICAL ONCOLOGY) EXAMINATION**

**AUGUST 2013**

The Tamil Nadu Dr.M.G.R Medical University

Chennai-600 032

# CERTIFICATE

This is to certify that **DR SUJAY SUSIKAR has** been a M.Ch Postgraduate student during the period August 2010 to August 2013 in the Department of Surgical Oncology, Kilpauk Medical College and Government Royapettah Hospital, Chennai.

This Dissertation titled **"Comparison of Preoperative chemotherapy with Paclitaxel and Cisplatin versus 5FU and Cisplatin in carcinoma Cervix stages IB2, IIA2 and IIB "** is a bonafide work done by him during the study p the Tamil Nadu Dr.M.G.R Medical University in partial Surgical Oncology Examination.

Dean

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Chennai - 10

**Prof. Dr.R.Rajaraman, M.S., M.Ch**

Professor and Head

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Kilpauk Medical College &

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Chennai

MASTER CHART

| No. | Name | Age | CD Number | Pre chemo Stage | Biopsy | Grade of tumor | Chemo Group | response after evaluation | tumor size in cm | blood loss in ml | operative time in min | right parametrium in mm | left parametrium in mm | number of nodes harvested- left | number of nodes harvested - right | vaginal cuff in mm | macroscopic residue in cervix in mm | microscopic residue in cervix | nodal positivity - right | nodal positivity - left |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | G | 38 | 1082/10 | II B | WDS | 1 | 1 | PR 1 | >4 | 200 | 130 | 18 | 20 | 12 | 15 | 32 | 11 | + | 0 | 0 |
| 2 | M | 42 | 1121/10 | II B | MDS | 2 | 1 | PD | >4 | | | | | | | | | | | |
| 3 | L | 50 | 1330/10 | IIB | WDS | 1 | 2 | PR 2 | >4 | 260 | 145 | 16 | 17 | 5 | 4 | 28 | 0 | + | 0 | 0 |
| 4 | M | 45 | 1329/10 | IB 2 | PDS | 3 | 2 | PR 1 | >4 | 280 | 135 | 24 | 16 | 5 | 11 | 34 | 34 | + | 0 | 0 |
| 5 | V | 37 | 1421/10 | II B | PDS | 3 | 2 | PR 1 | >4 | 320 | 190 | 20 | 18 | 7 | 10 | 26 | 28 | + | 0 | 0 |
| 6 | A | 55 | 1506/10 | IIB | PDS | 3 | 2 | PR 1 | <4 | 200 | 130 | 18 | 22 | 8 | 6 | 32 | 4 | + | 0 | 0 |
| 7 | S | 56 | 1547/10 | IIB | smS | 3 | 1 | CR | >4 | 150 | 120 | 22 | 20 | 6 | 7 | 30 | 0 | - | 0 | 0 |
| 8 | D | 38 | 30/11 | IIB | WDS | 1 | 2 | PR 1 | >4 | 400 | 200 | 18 | 16 | 3 | 5 | 24 | 28 | + | 0 | 0 |
| 9 | Y | 38 | 198/11 | IIB | PDS | 3 | 2 | SD | >4 | | | | | | | | | | | |
| 10 | V | 66 | 295/11 | IIB | WDS | 1 | 2 | CR | >4 | 240 | 100 | 22 | 17 | 8 | 7 | 22 | 0 | - | 0 | 0 |
| 11 | K | 34 | 297/11 | IIB | MDS | 2 | 1 | PR1 | >4 | 180 | 110 | 24 | 20 | 7 | 8 | 34 | 14 | + | 0 | 0 |
| 12 | P | 35 | 311/11 | IIB | PDS | 3 | 2 | SD | <4 | | | | | | | | | | | |
| 13 | S | 40 | 370/11 | IIB | WDS | 1 | 1 | CR | >4 | 340 | 130 | 22 | 24 | 10 | 9 | 35 | 0 | - | 0 | 0 |
| 14 | D | 36 | 406/11 | IIB | PDS | 3 | 2 | SD | >4 | | | | | | | | | | | |
| 15 | S | 50 | 432/11 | IIB | MDS | 2 | 2 | PR2 | >4 | 280 | 120 | 24 | 26 | 8 | 9 | 33 | 0 | + | 0 | 0 |
| 16 | V | 50 | 531/11 | IB 2 | WDS | 1 | 1 | PR1 | >4 | 240 | 100 | 22 | 24 | 7 | 9 | 35 | 8 | + | 0 | 0 |
| 17 | T | 40 | 541/11 | IIB | MDS | 2 | 2 | SD | <4 | | | | | | | | | | | |
| 18 | D | 47 | 731/11 | IIB | PDS | 3 | 1 | CR | >4 | 250 | 140 | 26 | 24 | 7 | 8 | 36 | 0 | - | 0 | 0 |
| 19 | S | 47 | 854/11 | IIB | Lcs | 1 | 2 | PR1 | >4 | 150 | 120 | 24 | 22 | 8 | 10 | 28 | 4 | + | 0 | 0 |
| 20 | L | 55 | 932/11 | IIB | WDS | 1 | 1 | PR1 | >4 | 600 | 200 | 24 | 14 | 12 | 10 | 34 | 0 | + | 0 | 0 |
| 21 | S | 65 | 972/11 | IIB | MDS | 2 | 2 | PR1 | >4 | 750 | 210 | 16 | 18 | 10 | 12 | 28 | 14 | + | 6 | 8 |
| 22 | S | 32 | 1000/11 | IB2 | MDS | 2 | 1 | CR | <4 | 240 | 90 | 24 | 26 | 6 | 8 | 30 | 0 | - | 0 | 0 |
| 23 | M | 48 | 1033/11 | IIB | smS | 3 | 2 | PR1 | >4 | 320 | 130 | 22 | 27 | 8 | 10 | 28 | 4 | + | 0 | 0 |
| 24 | L | 37 | 1066/11 | IIA 2 | WDS | 1 | 1 | PD | >4 | | | | | | | | | | | |
| 25 | B | 45 | 1178/11 | IB2 | MDS | 2 | 2 | PR1 | >4 | 700 | 180 | 24 | 22 | 9 | 7 | 30 | 0 | - | 4 | 0 |

MASTER CHART

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 | M | 40 | 1177/11 | IIA 2 | PDS | 3 | 1 | PR2 | >4 | 240 | 90 | 24 | 21 | 9 | 8 | 28 | 0 | - | 0 | 0 |
| 27 | S | 50 | 1162/11 | IB 1 | MDS | 2 | 2 | SD | >4 | | | | | | | | | | | |
| 28 | M | 50 | 1182/11 | II B | WDS | 1 | 2 | PR1 | >4 | 320 | 140 | 22 | 26 | 8 | 11 | 35 | 12 | + | 0 | 0 |
| 29 | S | 48 | 1195/11 | IIB | MDS | 2 | 1 | CR | >4 | 140 | 95 | 26 | 24 | 7 | 6 | 30 | 0 | - | 0 | 0 |
| 30 | N | 52 | 1308/11 | IIB | PDS | 3 | 2 | SD | >4 | | | | | | | | | | | |
| 31 | M | 52 | 1317/11 | IIA 2 | Lcs | 1 | 1 | SD | <4 | | | | | | | | | | | |
| 32 | K | 38 | 1347/11 | IB2 | MDS | 2 | 1 | PR1 | >4 | 400 | 150 | 22 | 28 | 9 | 11 | 28 | 11 | + | 0 | 0 |
| 33 | A | 41 | 1348/11 | IIB | PDS | 3 | 2 | PR1 | >4 | 260 | 130 | 24 | 26 | 12 | 9 | 32 | 8 | + | 0 | 0 |
| 34 | M | 40 | 1386/11 | IB2 | WDS | 1 | 1 | CR | >4 | 320 | 90 | 27 | 21 | 7 | 8 | 26 | 0 | - | 0 | 0 |
| 35 | M | 63 | 1376/11 | IIA 2 | smS | 3 | 2 | PR1 | >4 | 290 | 160 | 24 | 18 | 8 | 12 | 30 | 14 | + | 0 | 0 |
| 36 | V | 61 | 34/12 | IB 2 | MDS | 2 | 1 | PR 1 | >4 | 320 | 140 | 28 | 22 | 7 | 11 | 38 | 0 | + | 0 | 0 |
| 37 | K | 48 | 266/12 | IIB | MDS | 2 | 1 | PR1 | >4 | 270 | 120 | 24 | 22 | 6 | 9 | 28 | 8 | + | 0 | 0 |
| 38 | V | 40 | 287/12 | IIB | PDS | 3 | 1 | CR | <4 | 200 | 90 | 26 | 24 | 7 | 8 | 30 | 0 | - | 0 | 0 |
| 39 | P | 58 | 313/12 | IIB | WDS | 1 | 1 | CR | >4 | 270 | 140 | 24 | 24 | 8 | 10 | 28 | 0 | - | 0 | 0 |
| 40 | V | 48 | 331/12 | IIA 2 | Lcs | 1 | 1 | CR | >4 | 220 | 100 | 22 | 25 | 7 | 9 | 33 | 0 | - | 0 | 0 |
| 41 | P | 42 | 432/12 | IIB | PDS | 3 | 2 | SD | >4 | | | | | | | | | | | |
| 42 | L | 45 | 525/12 | IB2 | MDS | 2 | 2 | PR1 | >4 | 340 | 140 | 20 | 24 | 8 | 9 | 28 | 0 | + | 0 | 0 |
| 43 | L | 55 | 639/12 | IIB | WDS | 1 | 2 | SD | >4 | | | | | | | | | | | |
| 44 | S | 55 | 739/12 | IIB | PDS | 3 | 1 | CR | >4 | 270 | 120 | 24 | 30 | 9 | 11 | 27 | 0 | - | 0 | 0 |
| 45 | T | 43 | 763/12 | IIB | MDS | 2 | 1 | CR | >4 | 180 | 95 | 26 | 22 | 8 | 9 | 30 | 0 | - | 0 | 0 |
| 46 | V | 48 | 854/12 | IIB | PDS | 3 | 1 | PR 1 | >4 | 400 | 140 | 24 | 20 | 11 | 13 | 34 | 16 | + | 8 | 6 |
| 47 | V | 36 | 873/12 | IIB | WDS | 1 | 2 | PR2 | <4 | 220 | 130 | 22 | 24 | 9 | 8 | 26 | 8 | + | 0 | 0 |
| 48 | M | 36 | 1016/12 | IB2 | MDS | 2 | 1 | CR | >4 | 1200 | 220 | 24 | 20 | 7 | 8 | 30 | 0 | - | 0 | 0 |
| 49 | A | 47 | 1050/12 | IIB | PDS | 3 | 1 | SD | >4 | | | | | | | | | | | |
| 50 | J | 48 | 1076/12 | IIB | WDS | 1 | 2 | SD | >4 | | | | | | | | | | | |
| 51 | S | 46 | 1077/12 | IIA2 | MDS | 2 | 2 | SD | >4 | | | | | | | | | | | |
| 52 | A | 40 | 1081/12 | IB2 | PDS | 3 | 1 | SD | >4 | | | | | | | | | | | |
| 53 | M | 60 | 1085/12 | IIB | MDS | 2 | 2 | CR | >4 | 240 | 100 | 24 | 20 | 6 | 8 | 28 | 0 | - | 0 | 0 |
| 54 | M | 62 | 1095/12 | IIB | PDS | 3 | 1 | SD | >4 | | | | | | | | | | | |
| 55 | A | 42 | 2008/12 | IIB | MDS | 2 | 2 | CR | >4 | 340 | 130 | 26 | 24 | 9 | 8 | 34 | 0 | - | 0 | 0 |
| 56 | L | 52 | 2014/12 | IIB | PDS | 3 | 2 | PR 1 | <4 | 200 | 130 | 18 | 22 | 8 | 6 | 32 | 4 | + | 0 | 0 |

# DECLARATION

I solemnly declare that the dissertation titled "**Comparison of Preoperative chemotherapy with Paclitaxel and Cisplatin versus 5FU and Cisplatin in carcinoma Cervix stages IB2, IIA2 and IIB"** was done by me at Department of Surgical Oncology, Kilpauk Medical College and Government Royapettah Hospital, Chennai between August 2010 to February 2013 under the guidance and supervision of Prof. Dr. R.Rajaraman. The Dissertation is submitted to The Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment for the award of M.Ch.Degree (Branch VII) in Surgical Oncology.

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Date:

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# *CONTENTS*

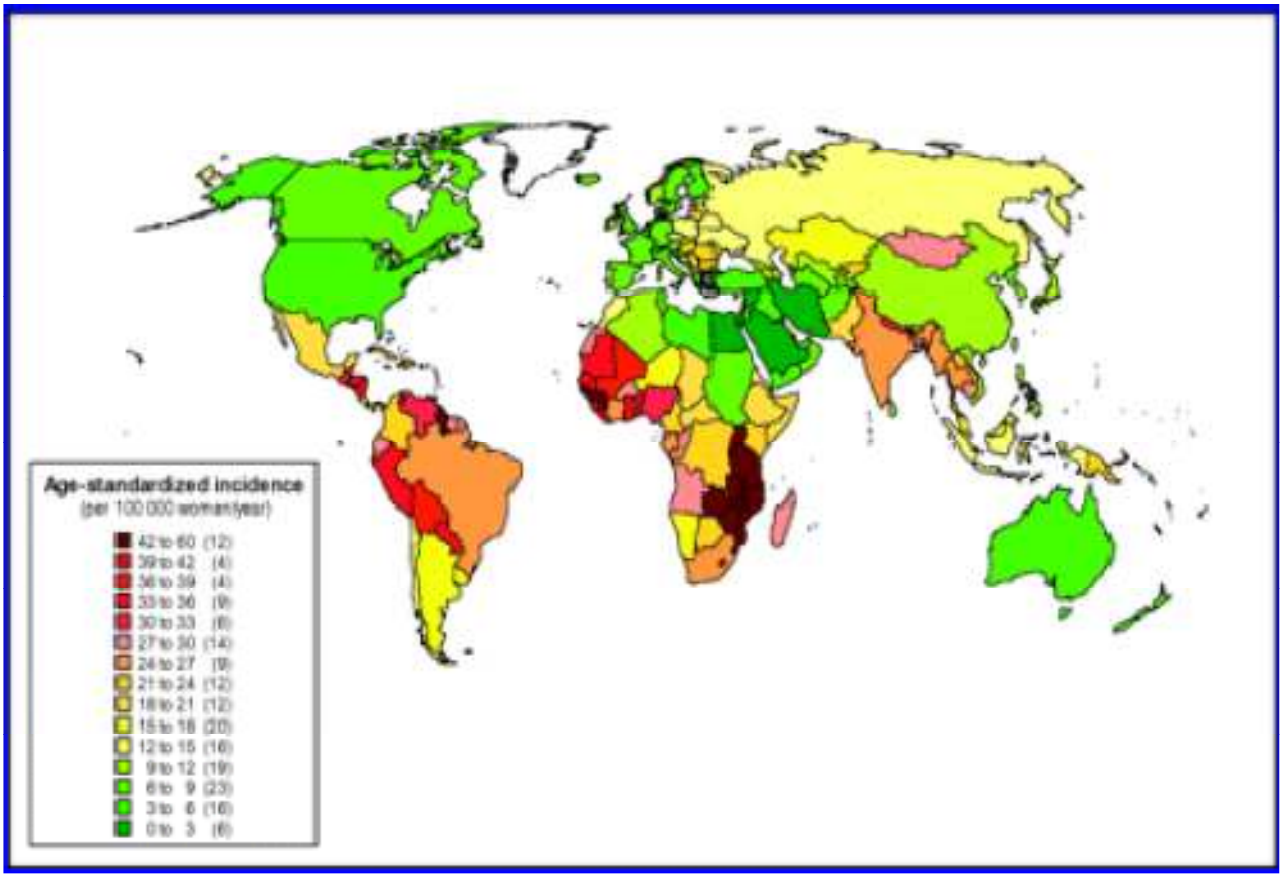
# INTRODUCTION

## EPIDEMIOLOGY OF CERVICAL CANCER WORLDWIDE

**C**ervical cancer is among the commonest cancers affecting women worldwide. It is the seventh commonest cancer affecting an estimated 530,000 new women in 2008, accounting for 4.2% among all cancers [1]. It is the third commonest cancer among women causing 8.8% of all cancers in women. In developing countries, it increases to 13% of all cancers in women [1]. The incidence and mortality rates are higher in low and middle income countries. Even in these countries, the highest incidence and mortality rates are seen in the low socio-economic groups which further exemplify the health inequity of this disease [2].

Cervical cancer tops the list among cancers among women in certain parts of Asia and Africa. The low risk regions are Western Asia, North America, Australia and New Zealand. Overall, the mortality rate is 52%.The estimated death due to cervical cancer was 275000 in 2008 and 88% of these occurred in developing countries [1] .**There is a seventeen fold difference in mortality due to cervical cancer among different regions of the world** [2].

# Worldwide distribution of Cervical Cancer



## THE BURDEN OF CERVICAL CANCER IN INDIA

Cervical cancer has been highly prevalent among women in India over the past few decades. India accounts for one fourth of the global burden of this disease.

Two population based cancer registries in our country have recorded highest incidence rates for cervical cancer. In the rest of the population based cancer registries, it is second only to breast cancer in incidence. The burden of cervical cancer in India is disproportionately high [3]. Cervical cancer is the third leading cause of cancer mortality. It accounts for 10% of all cancer mortality in India. Almost **26% of all cancer deaths in women are caused by cervical cancer.**

Chennai has the highest age adjusted incidence rates while Thiruvanathapuram in Kerala has the lowest age adjusted incidence rate .North eastern districts of Tamilnadu show a higher incidence compared to other districts in the state [ICMR].

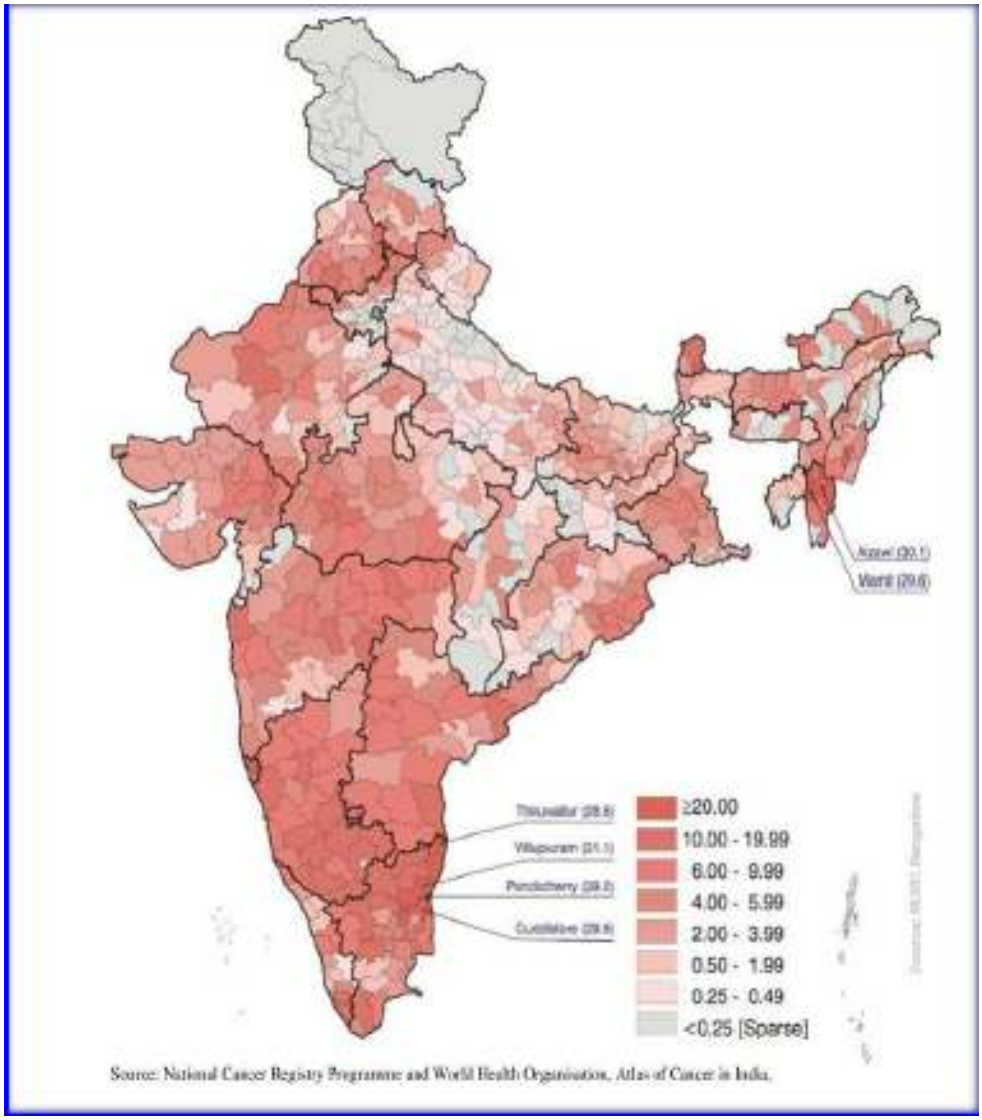
**Cervical Cancer Incidence in India**

| PBCR | CR | AAR |
|---|---|---|
| Bangalore | 14.3 | 18.8 |
| Barshi | 20.0 | 22.8 |
| Bhopal | 12.0 | 17.7 |
| Chennai | 20.3 | 22.3 |
| Delhi | 12.3 | 17.4 |
| Mumbai | 11.5 | 13.9 |
| Ahmedabad | 6.9 | 7.9 |
| Kolkata | 13.2 | 12.3 |
| Dibrugarh district | 3.8 | 5.1 |
| Kamrup urban district | 12.8 | 17.3 |
| Silchar town | 10.6 | 12.1 |
| Imphal west district | 17.2 | 20.5 |
| Mizoram state | 13.7 | 17.4 |
| Aizwal district | 20.6 | 25.4 |
| Sikkim state | 6.9 | 10.9 |

Crude rate(CR) and Age Adjusted Incidence rate(AAR) per 100,000 person for cancer cervix in population based cancer registries

The highest incidence of cervical cancer in our country is found in women in their late 40s and 50s.

The prevalence is higher in rural India and among women of low socio economic status. This may be due to lack of awareness of risk factors of the disease and poor access to health care facilities. Women from low socio economic status show poor compliance to treatment and follow up which further increases the mortality and morbidity from the disease.




Despite having had a diagnosis of cervical cancer, around 40% of patients registered in the Hospital Based Cancer Registries in Bangalore, Chennai and Mumbai did not complete their treatment at the reporting institution. Thus the most disadvantaged sections of Indian society are the worst victims of this debilitating disease.

Cervical cancer screening programs have reduced mortality and morbidity from the disease in the developed world but these success stories are not applicable to

developing countries like India because cytology based screening programmes demand facilities, expertise and equipment. Hence, death from this disease remains high in middle income countries, including India.

## ECONOMIC BURDEN OF CERVICAL CANCER

Cervical cancer patients lose a large part of their productive life because of long standing disability and early death. This disease is responsible for 2.7million (age weighted) Years of Life Lost (YLL) worldwide among women between the ages of 25 and 64, out of which 2.4million occur in developing countries. The Years of Life Lost (YLL) due to cervical cancer is greater than that caused by any other cancer in India. It accounts for 4% of total YYLs due to all causes in India. In India, the Years of Life Lost (YLL) due to cervical cancer were 936.3 in 2000, being among the highest in the world [4] .The high medical expenses and the mortality burden has a significant impact on the economic structure of families which in turn affects the individual and community at large. [4]

**Hence it becomes imperative to identify new prevention strategies to reduce the overall risk of cervical cancer, to design new methodologies to detect cancer early and to explore newer treatment options to improve the therapeutic outcome of cervical cancers.**

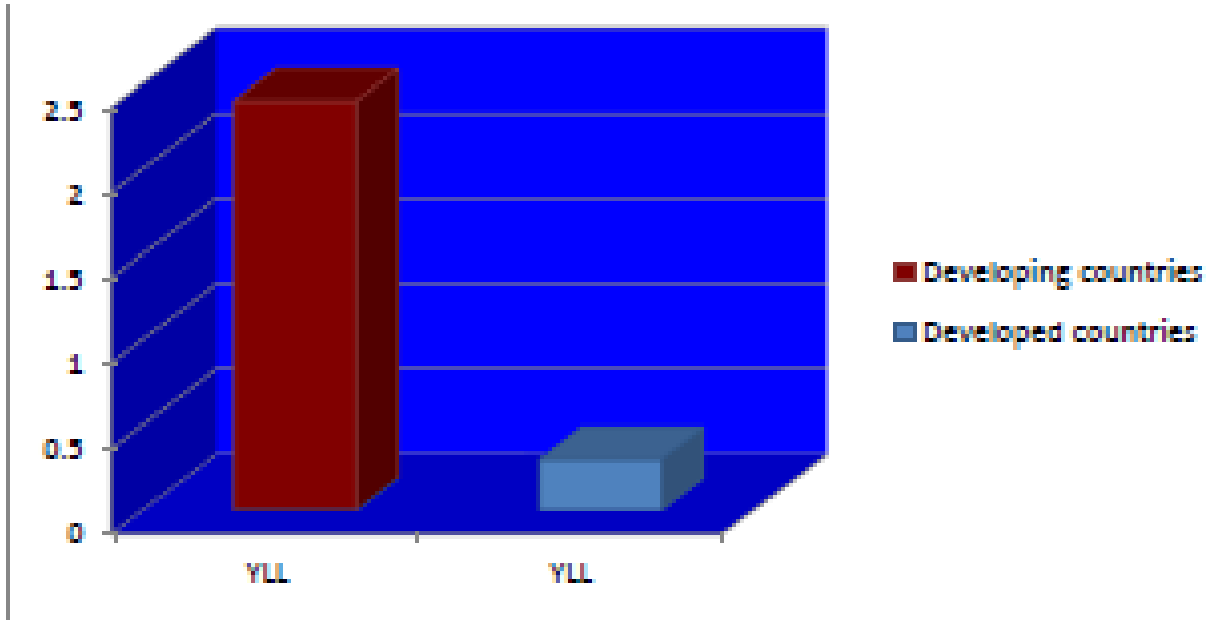



**Table showing Years of Life Lost**

# RISK FACTORS FOR CERVICAL CANCER

**Human Papilloma Virus:**

Cervical cancer behaves like a sexually transmitted disease in terms of risk factors. Several studies have shown that the causative agent of cervical cancer is infection with human papilloma virus [HPV]. HPV DNA is found in the majority of patients with invasive cervical cancer. More than 40 HPV types can infect the cervix.70% of cervical cancers are caused by HPV 16 and 18. The remaining cancers are caused by other high risk strains namely 31, 33, 35 etc. [5]. HPV infection occurs in 50% of men and women who are sexually active.

The series of steps involved in progression of HPV infection to invasive cancer are:

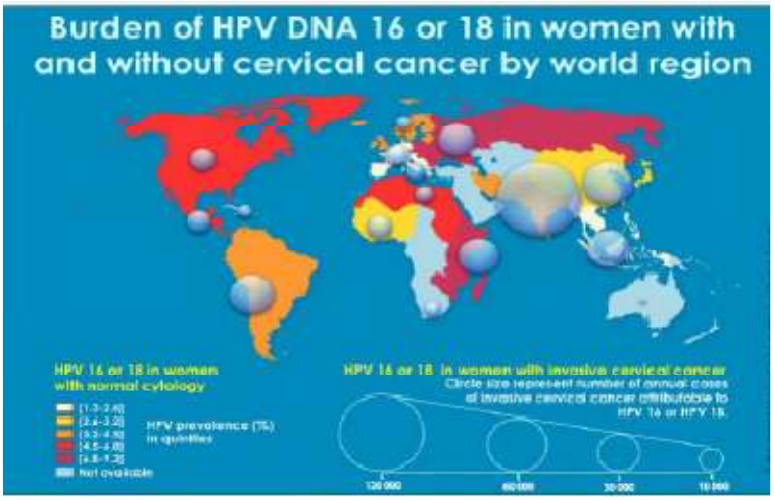
[1]HPV transmission

[2]Acute HPV infection

[3]Persistent HPV infection causing precancerous lesions

[4]Invasive cervical cancer

HPV infection resolves spontaneously in majority of women. Persistent infections are found in 3 – 10% of women and these women are at high risk of developing cervical cancer. In India, invasive cervical cancers are associated with HPV 16/18 in 82.5% of cases. Women with HPV infection have a 500 fold increase in the odds of having cervical cancer compared to women with no HPV infection [5].




**Female sexual behavior**

1. Age at first intercourse - Women who start their sexual life at an early age particularly before 16 years are at higher risk (2.4 fold increased risk) of developing cancer cervix [6]
2. Multiple sexual partners – women with promiscuous sexual behavior are at higher risk of developing cervical cancer. The risk of acquiring cervical cancer doubles when the number of sexual partners is more than 6.
3. Parity - Risk factors related to parity include age at first child birth and multiparity.

**Male sexual behavior (high risk male)**

. High risk male sexual habits, the presence of which is associated with a higher incidence of cancer cervix in their spouses are

1. Promiscuous behavior with >3 extra marital partners
2. History of sexually transmitted disease

3. History of penile cancer (increases risk of cancer cervix in wife by 3 – 6 times)[6]

***Lower socio-economic group***

Women from a lower socio-economic group have a higher incidence (about 3 fold) of cervical malignancy due to early marriage, early onset of sexual life and lack of genital hygiene.

***Smoking***

Smoking appears to double the risk of developing cervical cancer [7]. Smoking constituents have been detected in cervical mucus. Levels of nicotine were increased forty-fold and the major metabolite of nicotine, nicotinine levels were increased four-fold in the cervical mucus of women with CIN, compared to serum levels [8]. It was found that there was increased DNA damage in cervical epithelium of smokers, regardless of concomitant HPV infection [9].

## Staging of cancer cervix: (FIGO staging system, 2009 )

**Stage I : Carcinoma strictly confined to the cervix (extension to the corpus is disregarded)**

**Stage IA:** Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm

**Stage IA1:** Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
**Stage IA2:** Measured stromal invasion of >3.0 mm and ≤5.0 mm with an extension of not >7.0 mm

**Stage IB:** Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*

**Stage IB1:** Clinically visible lesion ≤4.0 cm in greatest dimension
**Stage IB2:** Clinically visible lesion >4.0 cm in greatest dimension

**Stage II: Cevical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina**

**Stage IIA:** Without parametrial invasion

**Stage IIA1:** Clinically visible lesion ≤4.0 cm in greatest dimension
**Stage IIA2:** Clinically visible lesion >4 cm in greatest dimension

**Stage IIB:** With obvious parametrial invasion

**Stage III: The tumor extends to the pelvic wall and/or involves lower third of the vagina and or causes hydronephrosis or non-functioning kidney****

**Stage IIIA:** Tumor involves lower third of the vagina, with no extension to the pelvic wall
**Stage IIIB:** Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

**Stage IV: The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.**

A bullous edema, as such, does not permit a case to be allotted to Stage IV

**Stage IVA:** Spread of the growth to adjacent organs.
**Stage IVB:** Spread to distant organs.

All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas.

Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular.

The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.

** On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

## OVERVIEW OF TREATMENT POLICY IN CANCER CERVIX [40, 42, 43]

All the three standard modalities of oncology namely radiation, surgery and chemotherapy have stamped their role in the treatment of different stages of the disease. An overview of current treatment recommendations for carcinoma of the cevix are given below.

**EARLY STAGE CERVICAL CANCER**

**FIGO Stage I A**

**Microinvasive carcinoma (invasion ≤ 5 mm):**

**Recommended work-up**

• Vaginal and rectal examination, exfoliative cytology (Papanicolaou smear), colposcopy, biopsy and/or endocervical curettage (ECC), conization or Loop electrosurgical procedure (LEEP)

• Histopathological finding with all standard tumor parameters

• Laboratory analyses: WBC, biochemical analyses

• Imaging: Chest X-ray, pelvic and abdominal ultrasound

**Diagnosis is based on conisation**

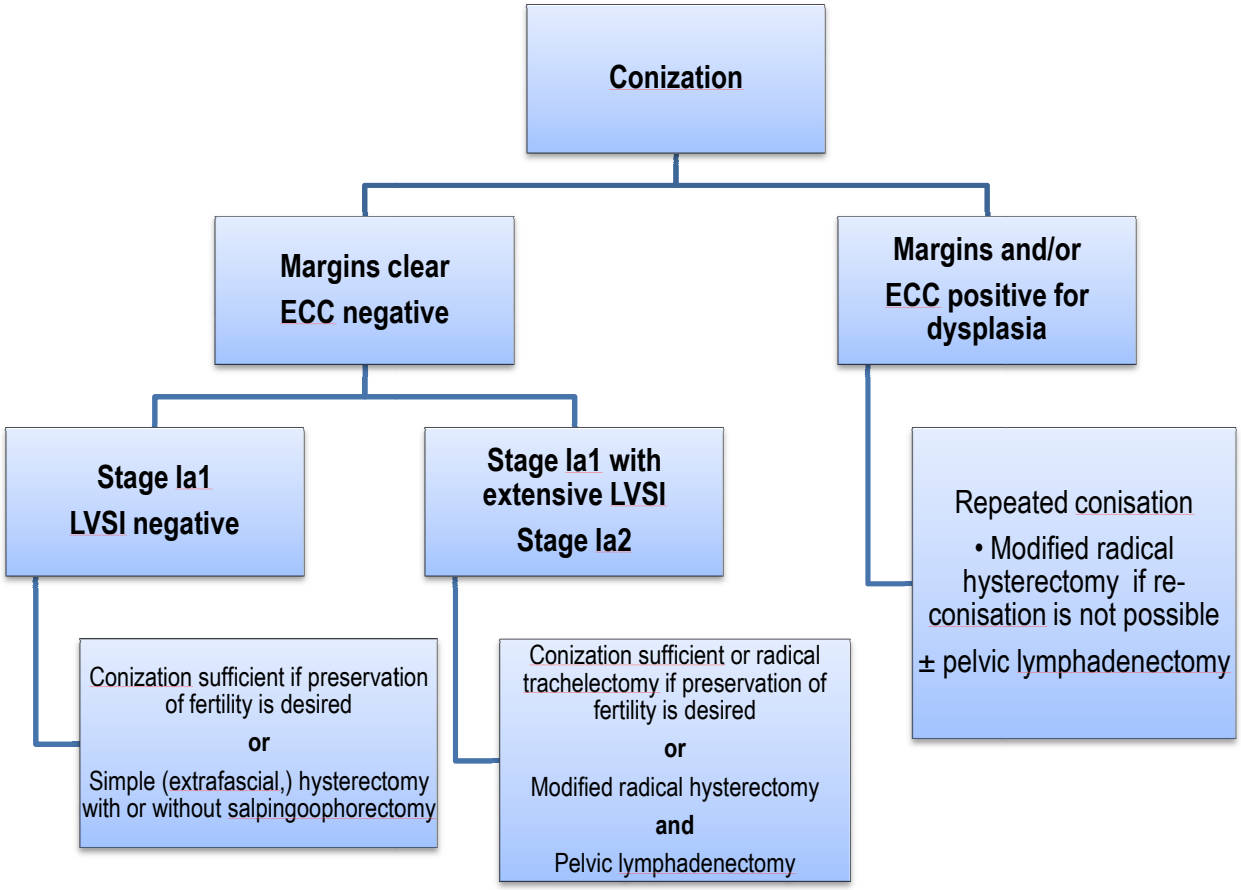
**Necessary Histo Pathologic parameters:**

- Depth of invasion
- Width of the tumor
- Tumor differentiation
- Lympho-vascular space invasion (LVSI)

- Resection margins

Microscopic stage IA disease is treated with surgery

## Management algorithm for stage IA (micro invasive - invasion <5mm):



**FIGO Stage Ib – II:**

**Recommended work-up**

**Neccessary investigations:**

1. Vaginal and rectal examination, colposcopy, biopsy and/or endocervical curettage (ECC); conization or loop electrosurgical procedure (LEEP) if needed for definitive diagnosis
2. Histopathological finding with all standard tumor parameters
3. Laboratory analyses: Complete hemogram, biochemical analyses including check for renal function and Hemoglobin
4. Imaging: Chest X-ray, abdominal and pelvic ultrasound (size and position of the tumor and tumor volume/cervix ratio)

**Optional investigations:**

1. Pelvic Magnetic Resonance Imaging
2. Computerized Tomography of the abdomen (PET/CT if possible)
3. Cystoscopy
4. Proctoscopy
5. Intra Venous Urogram or sonographic renal examination.
6. Involvement of the bladder or rectum should be confirmed histologically

. In early disease surgery is preferred over RT in:

1. Small volume disease (<4cm)
2. Younger patients for better preservation of sexual life as it preserves a pliable vagina.

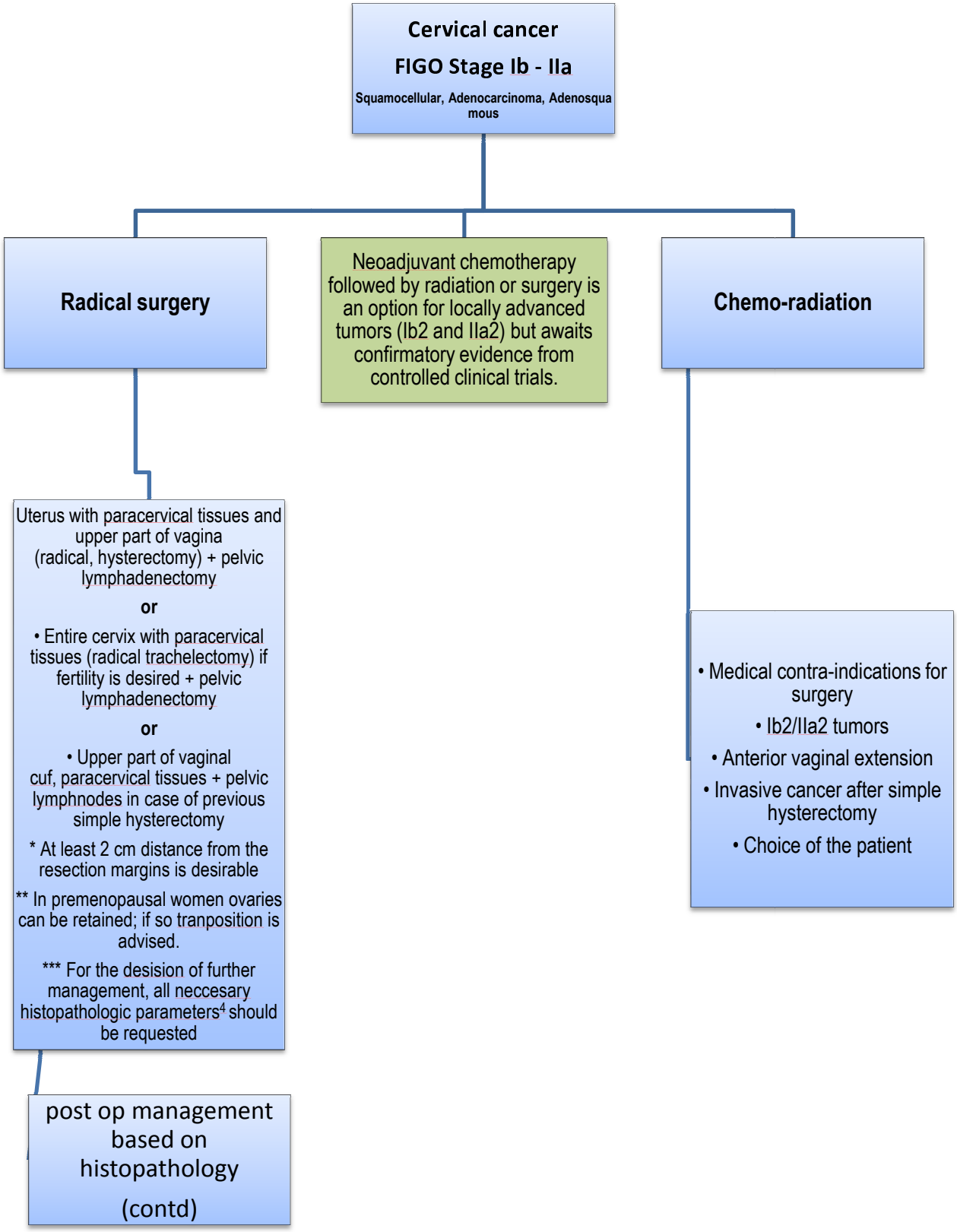
3. Endocervical cancers and adenocarcinomas due to reduced response rates of these histologies to RT
4. Patients with co-existing diseases like uterine myomas, ovarian cysts and prolapsed due to difficulty in optimal delivery of RT.

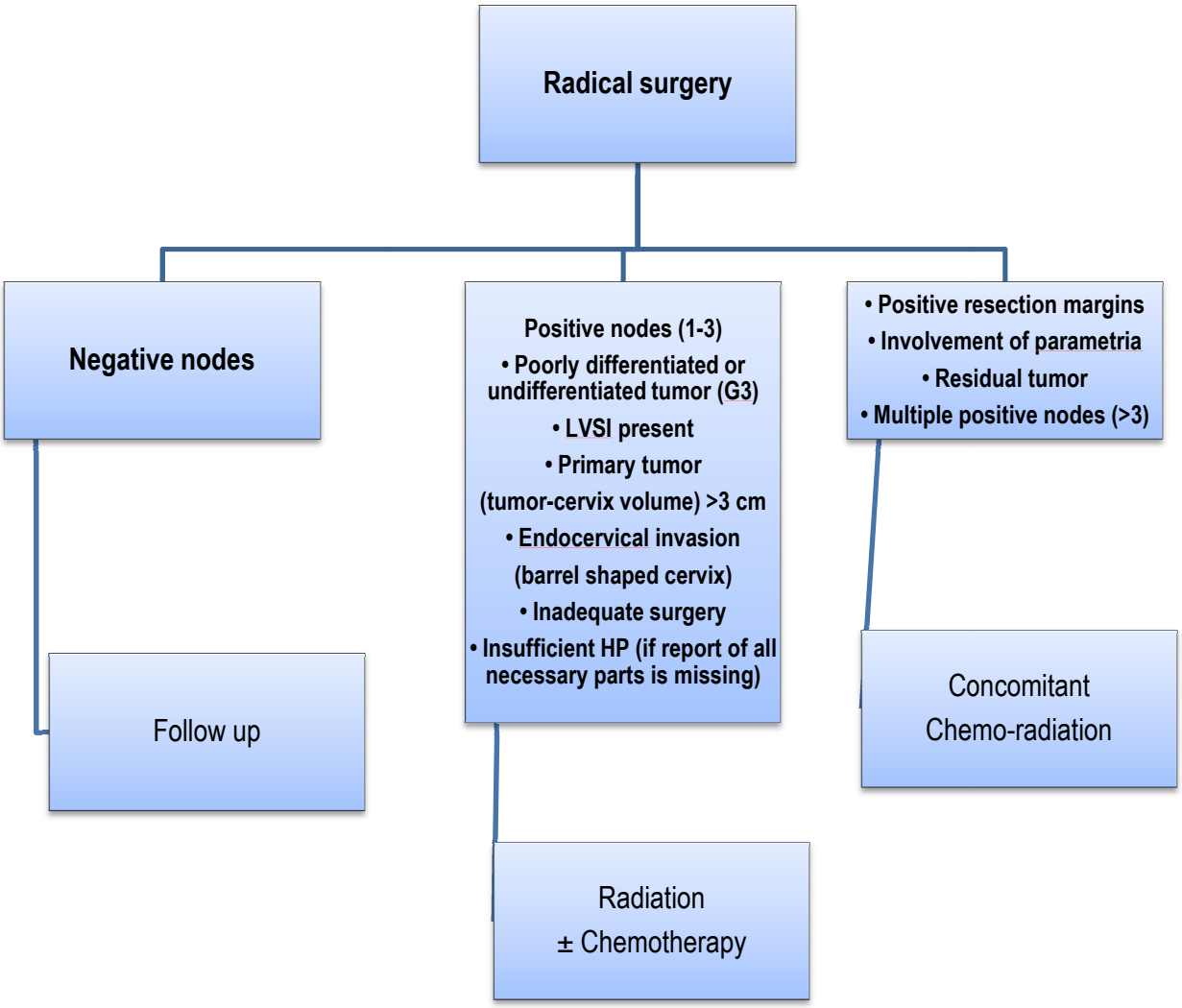
Advantages of surgery in early disease:

1. Surgery is both therapeutic and a staging procedure. Based on findings in the post-op specimen appropriate post-op RT can be combined to enhance cure rates.
2. Surgery preserves the ovaries if necessary and leaves behind a pliable vagina which preserves the sexual life of the patient.
3. Psychological relief to the patient that the disease has been cured is higher with surgery.

Radiotherapy is however also an effective alternative curative modality to surgery in early stage cervical cancer.

## Algorithm for stage Ib – II:



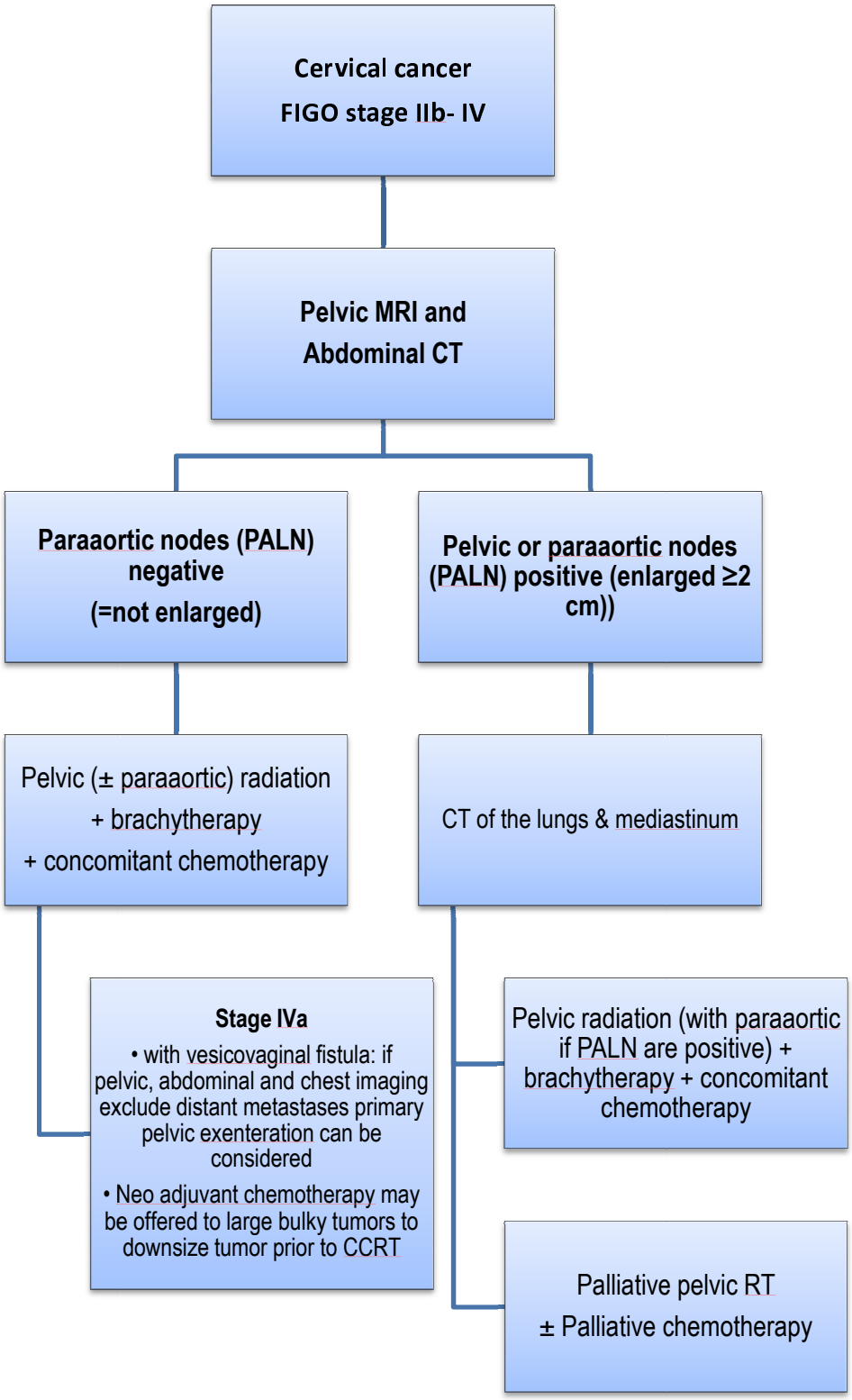

Radical surgery
Negative nodes
Positive nodes (1-3)
• Poorly differentiated or undifferentiated tumor (G3)
• LVSI present
• Primary tumor (tumor-cervix volume) >3 cm
• Endocervical invasion (barrel shaped cervix)
• Inadequate surgery
• Insufficient HP (if report of all necessary parts is missing)
• Positive resection margins
• Involvement of parametria
• Residual tumor
• Multiple positive nodes (>3)
Follow up
Radiation ± Chemotherapy
Concomitant Chemo-radiation

## Management of advanced stage disease:

## Cervical cancer FIGO stage IIB- IV:

### Recommended work-up

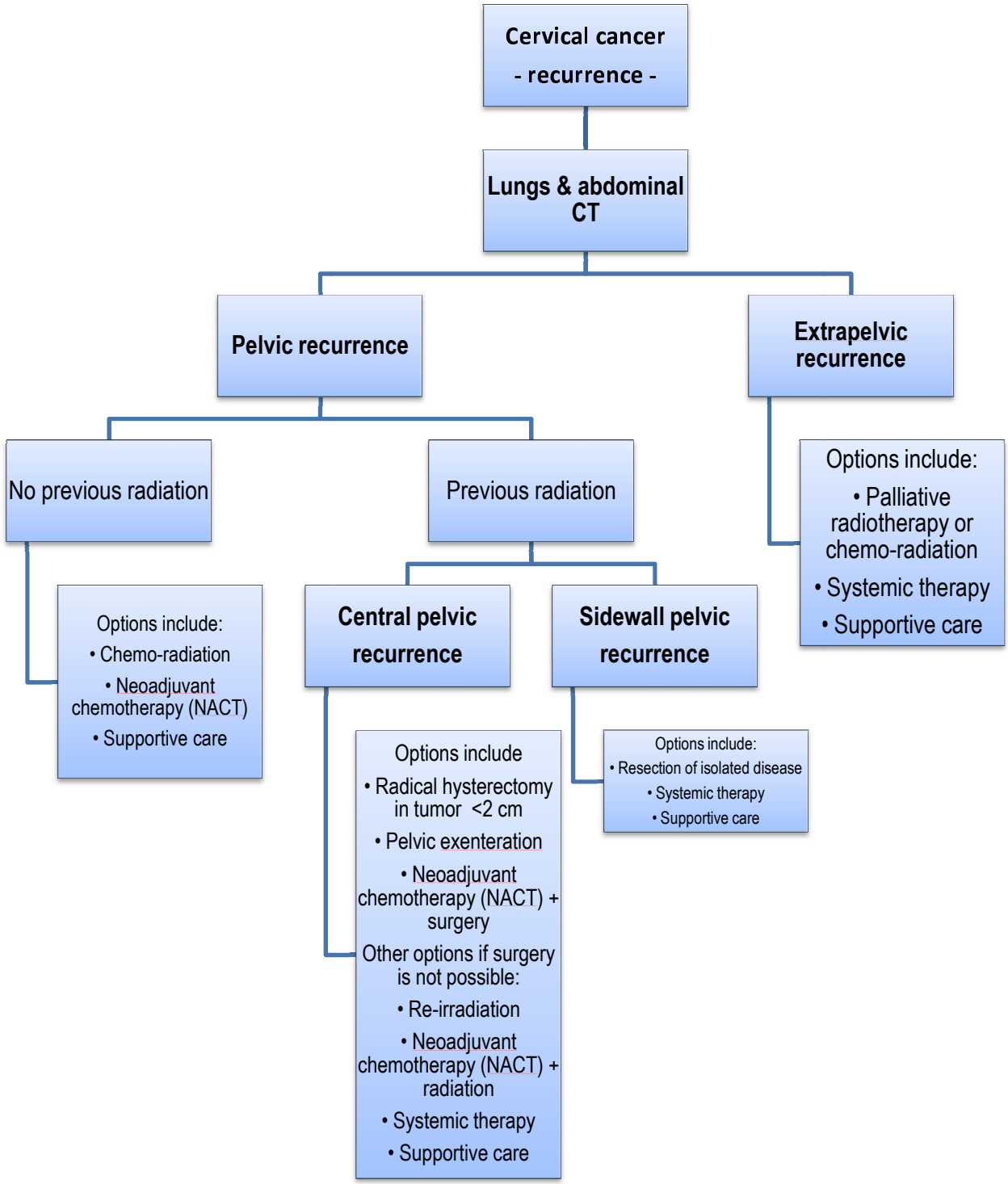
1. Vaginal and rectal examination, biopsy or endocervical curettage (ECC)
2. Histopathological finding with all standard tumor parameters
3. Laboratory analyses: WBC, biochemical analyses including check for renal function and Hb
4. Imaging: Chest X-ray, abdominal and pelvic ultrasound
5. Pelvic Magnetic Resonance imaging, CT of the abdomen (PET/CT if possible), cystoscopy, rectoscopy, IVU or sonographic renal examination. Involvement of the bladder or rectum should be confimed histologically


Cervical cancer
FIGO stage IIb- IV
Pelvic MRI and
Abdominal CT
Paraaortic nodes (PALN) negative
(=not enlarged)
Pelvic or paraaortic nodes (PALN) positive (enlarged ≥2 cm))
Pelvic (± paraaortic) radiation
+ brachytherapy
+ concomitant chemotherapy
CT of the lungs & mediastinum
Stage IVa
• with vesicovaginal fistula: if pelvic, abdominal and chest imaging exclude distant metastases primary pelvic exenteration can be considered
• Neo adjuvant chemotherapy may be offered to large bulky tumors to downsize tumor prior to CCRT
Pelvic radiation (with paraaortic if PALN are positive) + brachytherapy + concomitant chemotherapy
Palliative pelvic RT
± Palliative chemotherapy

## Management of recurrence:

### Recommended work-up

1. Vaginal and rectal examination, biopsy - histopathological confirmation of recurrence
2. Laboratory analyses: WBC, biochemical analyses including check for renal function and Hb
3. Imaging: Chest X-ray, pelvic and abdominal ultrasound, pelvic MRI and CT of the lungs and abdomen; (PET/CT if possible)
4. Cystoscopy, rectoscopy, IVU or sonographic renal examination


Cervical cancer
- recurrence -
Lungs & abdominal CT
Pelvic recurrence
Extrapelvic recurrence
No previous radiation
Previous radiation
Options include:
• Palliative radiotherapy or chemo-radiation
• Systemic therapy
• Supportive care
Options include:
• Chemo-radiation
• Neoadjuvant chemotherapy (NACT)
• Supportive care
Central pelvic recurrence
Sidewall pelvic recurrence
Options include
• Radical hysterectomy in tumor <2 cm
• Pelvic exenteration
• Neoadjuvant chemotherapy (NACT) + surgery
Other options if surgery is not possible:
• Re-irradiation
• Neoadjuvant chemotherapy (NACT) + radiation
• Systemic therapy
• Supportive care
Options include:
• Resection of isolated disease
• Systemic therapy
• Supportive care

## MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

Concomitant chemo radiotherapy remains the standard for locally advanced cervical cancer. An individual patient data meta analysis demonstrated an absolute 5-year survival benefit of 6% (from 60% to 66%) and 5-year disease-free survival benefit of 8% with chemo radiotherapy compared with radical RT alone. Patients with stage IB – IIA had a 5 year survival benefit of 10% with chemo radiotherapy. The survival benefit was 7% for stage IIB cancers and 3% for stage III – IVA. Mono therapy with cisplatin 40mg/m2 weekly is the preferred regimen. However, chemo radiotherapy is associated with increased gastrointestinal and hematologic toxicity.

### NOVEL APPROACHES

Exclusive chemoradiation is currently the gold standard of treatment in locally advanced cervical cancer. However, 5yr survival of patients treated for cervical cancer is still only around 70%. Hence there is a compelling need to improve the outcomes of locally advanced forms of this disease.

Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 2002-2008 [SEER]

| STAGE AT DIAGNOSIS | STAGE DISTRIBUTION (%) | 5YRRELATIVESURVIVAL (%) |
|---|---|---|
| LOCALIZED | 47 | 90.7 |
| REGIONAL | 36 | 56.7 |
| DISTANT | 12 | 16.2 |
| UNKNOWN | 4 | 54.8 |

This causes a concern that chemo radiation might be insufficient to eradicate bulky tumors. To address this issue, several different approaches like

i. Addition of newer chemotherapeutic agents,
ii. Neoadjuvant chemotherapy
iii. Altered fractionation schedules and
iv. Tri-modality treatments, including radio-therapy, chemotherapy and surgery, have been investigated.

Potential benefits of neoadjuvant therapy:

There are several potential benefits of neoadjuvant chemotherapy followed by surgery

i. Downsize the tumor,
ii. Render bulky tumors (International Federation of Gynecology and Obstetrics [FIGO] stages IB 2, IIA 2 and IIB) safe for surgery

iii. When a pelvic recurrence occurs RT would be an open option.

iv. It can eradicate or biologically alter micro metastases

In view of economic implications, availability of radiotherapy centres and radiotherapy induced morbidity, the advantages of downsizing the disease without the use of irradiation are tempting and open a completely new philosophy of radical treatment for locally advanced cervical cancer.

Pathologic complete response rates achieved with neoadjuvant strategies have proven to be an important determinant of long term survival in trials investigating neoadjuvant modalities.

Thus better neoadjuvant modalities would increase the pathological complete response rates and improve survival.

**PROGNOSTIC FACTORS**

Identification of factors of possible prognostic significance may help the clinician in tailoring treatment. Patients with a low risk of recurrence may be subjected to less intensive treatment whereas patients with a high risk of recurrence may be eligible for clinical trials.

**TUMOR FACTORS**

1. **Stage of the disease** has been found to be a strong prognostic factor. As the stage advances, the prognosis becomes worse. Numerous studies have indicated tumor size as a strong prognostic indicator for both early and locally advanced cervical cancer.

2. **Tumor size more than 4 cm** has been defined as bulky cervical cancer by FIGO and 10 year actuarial pelvic failure rates are found to be higher in patients with bulky cervical cancers. Another strong prognostic indicator is depth of invasion.
3. **Lympho vascular space invasion** is a classical prognostic parameter in early stages.
4. **Presence of lymph node metastases** has been proven to be of prognostic importance in several studies.
5. **Depth of tumor invasion determines** the incidence of pelvic lymph node metastases and, in advanced stages; tumor volume determines the incidence of lymph node metastases.
6. **Extent of parametrial involvement** was found to correlate adversely with survival. A retrospective study done by Kovalic et al, reported lower 10 year disease free survival in stage IIB disease with lateral half of parametrial involvement compared to medial half of parametrial involvement ( 52% Vs 68%, p value = 0.004). Stage IIB patients whose disease extended into the lateral parametrium had higher total pelvic failure rates. The 10 year disease free survival was lower in patients with stage IIIB cancers with bilateral parametrial invasion compared to unilateral parametrial invasion [10].
7. **Histologic subtype**: No significant difference in 5 year survival among patients with squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma [11]. However there are conflicting reports in the literature regarding the importance of histologic subtype as a predictor of overall survival in patients with cervical cancer.

8. **Grade of the tumor**: In contrast to other epithelial malignancies where histologic grading is an established prognostic factor, microscopic grading of cervical cancers has no prognostic value [12]
9. **Overall treatment time** is a critical parameter which determines treatment outcome. Loss of local control and survival of 1% per day when treatment exceeded 52 days has been reported in studies [13].
10. **HPV Genotype**: There is controversial data in the literature regarding the relationship of HPV genotype to prognosis in cervical cancer. However recent evidence suggests that HPV 18 positive cancers are associated with poor prognosis [14]. Elucidation of the mechanism involved in such association could lead to newer treatment approaches.

**HOST FACTORS**

1. **Lower socioeconomic status**: Lower socioeconomic status and poorer survival has been associated from several studies. Poverty and lower education has been associated with increased cervical cancer mortality [15].
2. **Hemoglobin levels**: In multivariate analysis, lower hemoglobin status at the time of diagnosis was associated with worse overall and disease free survival. The impact of declining hemoglobin level during Radiotherapy on the final outcome was not observed in multivariate analysis [16].
3. **Smoking** is a predictor of worse overall survival in patients with locally advanced cervical cancer treated with chemoradiation. Median survival was found to be 15 months shorter for smokers. Smoking was linked to increased cervical cancer

mortality in 3 of 5 survival analysis. A recent report found that smokers with high risk HPV positive cervical cancers were four times more likely to die of cervical cancer [9].

**Recommended follow-up**

- Every 3 months for two years or more often if clinically indicated.
- Every 4-6 months thereafter.
- Annually afterwards.
    - Investigations in addition to gynaecological examination should be performed depending on symptoms, local findings and general condition of the patient

# LITERATURE REVIEW

Cervical carcinoma remains among the most common and lethal malignancies in women world over [17]. In early stages of the disease, surgery and radiation are equally effective treatment modalities conferring good results [18]; but by themselves, these treatment modalities in locally advanced cases are suboptimal. The most common failures are pelvic with or without systemic relapses.

In the last decade, seven of eight prospective randomized phase III trials (18 – 22) have shown that concurrent chemoradiation is superior to standard radiation alone in bulky and locally advanced cervical cancers making it the new standard of care in the treatment of this group of cervical cancers.

Despite these recent encouraging results of concomitant chemoradiation based on cisplatin [18 - 22] or other radio sensitizing drugs there has been a high rate of disease recurrences - most commonly pelvic sometimes with distant metastases[20, 21]. This fact emphasizes the need to try newer treatment modalities to improve survival both overall and disease free.

Neoadjuvant chemotherapy is used in several solid tumors like breast and ovary but in cervical carcinoma its role still remains experimental. This may be due to the initial setback seen with this modality in the management of cervical cancer where the local treatment modality used after the chemotherapy was radiotherapy. The results of this sequence of treatment were not very promising and neoadjuvant chemotherapy took a back seat. Thus the local treatment modality used after induction chemotherapy is important.

Despite the fact that there is a lack of randomized trials comparing radiation upfront with radical surgery after neoadjuvant chemotherapy, emerging data from trials suggest that surgery may be a better modality after chemotherapy as it bypasses the cross-resistance between chemotherapy and radiation [23,24]. Furthermore both radiotherapy and chemotherapy function by first order kinetics while surgery works with zero order kinetics and eliminates residual disease in totality.

Several phase III randomized trials have demonstrated the superiority of neoadjuvant chemotherapy and surgery over radiation alone [24–28]. In a large, Italian, prospective study (29), patients with locally advanced cervical cancer were randomized received neoadjuvant chemotherapy followed with surgery or to standard treatment with definitive radiation. There was a 10% - 15% survival advantage among patients who had neoadjuvant therapy followed with surgery. Patients with tumors sized less than 4 cm did not appear to benefit from this approach as these were amenable to radical resection even at presentation.

But now considering the fact that concurrent chemoradiation is superior to radiation alone [18], neoadjuvant chemotherapy needs to compared with concurrent chemoradiation. Awaiting confirmation from phase III trials, two phase II studies that compared neoadjuvant chemotherapy followed with surgery versus standard chemoradiation have reported that both these modalities are similar in terms of survival [29].

Neoadjuvant chemotherapy looks to be a good alternative to surgery and irradiation for initial treatment of locally advanced cervical cancer. The potential benefits of this approach are:

i. It eradicates micrometastases
ii. Debulks tumors
iii. Renders inoperable tumors (international federation of gynecology and obstetrics [figo] stages ib2, iia2, iib to iiib) operable without radiotherapy
iv. Radiotherapy may be kept in reserve as salvage if a pelvic recurrence occurs
v. Surgery can overcome the cross-resistance that occurs between chemotherapy and radiation when they are delivered sequentially

This aspect of downstaging disease without irradiation is attractive and offers a totally new philosophy of treatment for locally advanced cervical cancer.

Resectability of locally advanced cervical tumors depends on the response to induction chemotherapy as seen from various studies [30]. The benefit of neoadjuvant chemotherapy on survival in solid tumors is mostly seen in cases with complete clinical or pathological response after the chemotherapy. The employment of an effective regimen of chemotherapy is thus necessary to obtain better survival figures [26–28].

Alessandro Buda et al (31) from the Istituto "Mario Negri, Milan compared 2 regimes of taxol , ifosfamide and platin( TIP) versus ifosfamide and platin (IP) alone and found that The former regimen was associated with higher response rates than the latter regimen.

There was no statistically significant effect on overall survival. They reported that a significant prognostic factor for survival was the optimal pathologic response.

A trial is undergoing using 4-epidoxorubincin which is active against advanced or recurrent cervical cancer. It was given before and after treatment for a total of six courses. Other chemotherapeutic regimens like cis-platinum alone or in combination with bleomycin and/or methotrexate have been shown to be effective in reducing the primary tumour bulk.(29, 30) Park et al. gave cis-platinum and 5-flurouracil before radiotherapy treatment of patients with poor prognostic factors and showed better survival in the neoadjuvant chemotherapy group. Randomized control studies are required to decide on the usefulness of neoadjuvant chemotherapy and on the best chemotherapeutic regimen.

Linghu et al ( 32) from , First Affiliated Hospital, Chongqing, China investigated on one hundred and forty-five patients with cervical squamous cancer stages Ib-IIa , among which 17 patients with bulky tumors (> or = 4 cm) were treated with cisplatin-based chemotherapy for 1-2 courses followed with radical hysterectomy and pelvic lymphadenectomy. The change of tumor size, pelvic lymph nodes metastasis, cervical wall invasion, the involvement of surgical specimen margin, and the blood loss during operation were assessed after operation and compared with those in 51 patients with bulky tumors and 77 patients with small local tumors who underwent surgery directly. Their study showed that

(1) The tumor size of 17 patients in the first group was decreased in various degrees after chemotherapy, with 13 patients of clinical effectiveness (76.47%).

(2) Post-operative histology has showed that patients with bulky disease have higher incidence of lymph node metastasis and deep cervical infiltration (5/68 and 3/68, respectively) than small tumors (1/77 and 1/77, respectively).

(3) Blood loss during operation in preop chemotherapy group was less than upfront surgery.

These authors concluded that most patients with bulky early stage cervical squamous carcinoma were sensitive to cisplatin-based chemotherapy, which was effective in greatly reducing local tumor size which in turn facilitated surgery by reducing blood loss.

Tanaka et al (33) from Wakayama Medical University, Japan studied preoperative irinotecan HCl (CPT-11) chemotherapy in patients with unresectable Stage IIIb cervical carcinoma. All 11 patients showed partial responses in tumor size reduction, and radical hysterectomy could be successfully performed in ten patients treated with CPT-11 and mitomycin C (MMC). One had retroperitoneal cancer progression during chemotherapy.

Chen H et al (34) of Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, China studied the efficacy of Neoadjuvant chemotherapy with short cycle-length, high-dose agents for locally advanced cancer cervix. **They reported that** preoperative neoadjuvant chemotherapy was well tolerated and was useful to reduce tumor size, eliminate pathological risk factors, and improve prognosis in responders

Hong-Bing Cai (35) ,et al from Zhong Nan Hospital, Wuhan University, China did a trial of 106 women with cervical cancer stage IB who received either neoadjuvant chemotherapy ($n$ = 52) or underwent primary surgery ($n$ = 54). The clinical response rate was 84.6% including a complete response (CR) in four patients (7.7%), partial

response (PR) in 40 patients (76.9%), and stable disease (SD) in eight patients (15.4%). Surgery showed positive nodes in 9.6% neoadjuvant chemotherapy group patients and in 29.6% of the primary surgery group patients ($P = 0.014$). Similar results were seen with vascular space involvement: 27.8% in the primary surgery arm compared with 9.6% in the neoadjuvant chemotherapy group ($P = 0.024$). Parametrial infiltration was seen in 7.4% of the patients in the primary surgery arm, while only 3.8% showed it in the neoadjuvant chemotherapy arm ($P = 0.679$). The 5-year survival rate was significantly higher for all patients who received neoadjuvant chemotherapy (84.6%) than for the control group (75.9%) ($P = 0.0112$). These authors concluded that neoadjuvant chemotherapy can be used to effectively eliminate pathological risk factors thus improving long-term survival in patients with locally advanced cervical cancer.

Mori T, Hosokawa K, Sawada M et al(35) from Kamigyo-ku, Kyoto, Japan studied 30 patientswith cervical cancer stage IB2 to IIIB who received paclitaxel (60 mg/m) and carboplatin (area under the curve, 2) every week for 6 cycles. Radical hysterectomy was performed 6 days after the final cycle of neoadjuvant chemotherapy. These patients were followed up, and the 5-year progression-free survivals (PFS) and overall survivals (OS) analyzed. The 5-year PFS and OS for patients were 79.2% and 83.1%, respectively, which were comparable to the outcomes of concurrent chemoradiation therapy. Larger tumor size and lymph node metastasis negatively correlated with survival. They concluded that preoperative chemotherapy with paclitaxel and carboplatin on a weekly schedule followed with radical surgery for patients with locally advanced cervical cancer is a promising mode of therapy that may improve the prognosis

35 patients with stage Ib, IIa, and IIb bulky carcinoma of cervix (> 4 cm) were treated with preoperative chemotherapy using a combination of vinblastine, bleomycin, and *cis*-platinum (VBP, 1 - 5 courses) followed with radical surgery at the School of Medicine, The Hanyang University, Seoul, Korea by Doo Sang Kim M.D et al.(37). The effectiveness of the chemotheapy was evaluated in the surgical specimen. The response rate was 89% and included a complete response in 16 patients (46%) and partial response in 15 (43%). There was no difference in the response rate by age, stage, or the geographic contour of the tumor. The number of courses of chemotherapy correlated with the response of the primary tumor ($P$ = 0.0004) up to a maximum three courses. In 15 patients with stage IIb, 11 patients (73%) had a stage-down. Lymphnode metastases were found in 26% of the patients after chemotherapy. All nodal metastases were seen in patients who had a partial response or a stable disease, and none in patients with complete responses ($P$ = 0.0029). This study suggested that preoperative chemotherapy before surgery was effective in reducing tumor volume or stage offering better conditions for surgery, and maybe eliminating micro metastases and disease in lymph nodes and possibly. The authors suggested that preoperative chemotherapy was effective

(1) In reducing tumor volume or the stage of the disease,

(2) In curing the lymph node involvement, and

(3) In improving the 2-year tumor-free survival rate.

**Current status of Neoadjuvant chemotherapy in carcinoma cervix:**

Neoadjuvant chemotherapy before surgery is an accepted treatment for locally advanced stages of cervical cancer in many parts of the world. The advantage of chemotherapy in these patients is

i. The potential significant reduction in tumor burden,
ii. Facilitating surgical excision in previously inoperable tumors.
iii. This approach also may obviate the need for radiation therapy if surgical margins are negative

This may become the standard of care in regions of the world where radiotherapy facilities are limited. Trials of neoadjuvant chemotherapy have also demonstrated an increased effectiveness without increases in surgical complication rates. (22, 23, 38, 39). Response of the tumor to chemotherapy is an important prognostic factor for survival. (30)

The optimal chemotherapy regimen is yet to be defined.

# AIM OF THE STUDY

Aims of this study were

1. To assess the efficacy of neoadjuvant chemotherapy followed with radical hysterectomy as an alternative to irradiation in bulky carcinoma cervix
2. To compare 2 two drug regimens- (Paclitaxel and Cisplatin with 5FU and cisplatin)
3. To assess if pathologic response has prognostic value on survival.

# PATIENTS AND METHODS

**Eligibility and Random Assignment:**

Patients with histologically confirmed bulky cervical Squamous cell carcinoma (FIGO stage IB2 to IIB) were included in the study.

Pretreatment evaluation included

1. History,
2. Physical examination,
3. Biopsy,
4. Complete blood analysis,
5. Chest x-ray and
6. Examination under anesthesia. By two examiners, with a third examiner to reach a consensus in case of disagreement
7. Tumor imaging by means of ultrasound of the abdomen and pelvis and contrast enhanced CT of the pelvis to determine the extent of disease.
8. Tumors involving the anterior fornix were evaluated with a cystoscopic examination and tumors involving the posterior fornix with proctoscopic examination based on findings on examination under anesthesia.

**Inclusion criteria:**

i. Age 18–65 years;

ii. Karnofsky performance status of ≥70%;

iii. Stages IB2( bulky IB- >4cm) ,IIA2( bulky IIA - >4cm) and IIB (parametrial involvement short of pelvic side wall)

iv. Normal hematological and renal function: hematological, Hb ≥10 g/l (patients were transfused to reach this hemoglobin); leukocytes more than 4000/$mm^3$; platelets more than 100000/$mm^3$; and normal blood urea and creatinine;

v. A normal chest x-ray

vi. No para aortic nodes or other secondaries on CECT abdomen

**Exclusion ciriteria**:

i. Other histologies, such as adenocarcinoma, adenosquamous carcinoma, neuroendocrine small cell carcinoma, lymphoma, sarcoma and other rare histologies

ii. Stages IA, IB1, III and IV

iii. Severe or uncontrolled infection or other systemic diseases

iv. Concomitant treatment with any experimental drug

v. Pregnant or nursing women

vi. Mental illness

vii. Previous or concomitant malignant diseases other than non-melanoma skin cancer

## Neoadjuvant Chemotherapy Regimens:

**The patients who were evaluated and found fit for the protocol (adhering to all the inclusion criteria and excluding all exclusion criteria) were randomized to either of the two chemotherapy regimens**

The Taxol +Platin regimen was administered as follows: Paclitaxel given at the dose of 175 mg/$m^2$ as a 3-hour infusion on day 1. Premedication given to reduce the risk of Paclitaxel hypersensitivity was as follows: Dexamethasone 8 mg intravenously 60 minutes before and chlorpheniramine 10 mg, Ondansetron 8mg and Ranitidine 150 mg intravenously 30 minutes before treatment delivery. Cisplatin 75 mg/$m^2$ was be administered on day 2 as a 60-minute infusion after prehydration with 1 L of normal saline and premedication with Dexamethasone 8 mg intravenously 60 minutes before and Ondansetron 8mg and Ranitidine 150 mg intravenously 30 minutes before treatment delivery . Hydration with 3 L of 5% dextrose solution during 24 hours was infused simultaneously.

The 5 Fluoro uracil + cisplatin regimen was administered as follows: 5-Fluoro uracil at a dose of 500mg/$m^2$ as a 3- hour infusion. Premedication given to reduce the risk of 5-FU toxicity was as follows: Dexamethasone 8 mg intravenously 60 minutes before and Ondansetron 8 mg and Ranitidine 150 mg intravenously 30 minutes before treatment delivery. Cisplatin 75 mg/$m^2$ was administered on day 2 as a 60-minute infusion after prehydration with 1 L of normal saline and premedication with Dexamethasone 8 mg intravenously 60 minutes before and Ondansetron 8mg and Ranitidine 150 mg intravenously 30 minutes before treatment delivery followed by post-hydration with 1 L of 5% dextrose solution over 2 hours.

In both arms, treatment was administered every 3 weeks for a total of three courses.

**Treatment Modifications**

Complete Blood Counts were performed 3 weekly or more often if toxicity occurred; evaluation of renal function was repeated before each cycle.

Treatment administration was based on evaluation of hemoglobin and blood cell counts before the start of each cycle. Treatment was administered only if the Hemoglobin was more than 10g/dl, Total WBC Count was more than 4000/μL and the platelet count more than 100,000/μL. Treatment was delayed week to week until minimum hematologic parameters are met. After two consecutive treatment delays, on the basis of physician judgment, treatment was either discontinued or continued. Delays were not permitted other than for documented toxicity.

**Treatment after Neoadjuvant Chemotherapy**

Tumor response was assessed clinically (Abdominal, vaginal and Rectal examination) and by CT after three courses and all patients with adequate response that was deemed operable (with supple parametria, decrease in bulk of cervix and lower two thirds of vagina free such that radical hysterectomy maybe done achieving negative margins) underwent radical hysterectomy and pelvic lymphadenectomy within 3 or 4 weeks after the administration of the third cycle.

**Radical hysterectomy procedure**

Under general anesthesia, laparotomy was done using a lower midline/vertical incision. Lateral pelvic peritoneum was incised, retroperitoneal plane was created and ureters were identified. Infundibulo pelvic and round ligament was ligated and divided at the

pelvic brim. Peritoneal incision was extended anteriorly up to uterovesical fold. Cervico vesical septum was identified divided sharply and bladder pushed down away from cervix and vagina. Ureters were traced down to Wertheim's ureteric canal preserving mesoureter. Pararectal and paravesical fossae were created by entering the plane between pelvic side wall, internal iliac vessels and the ureter down to the levator ani. Uterine artery was origin identified and ligated and divided at its origin. Ureteric tunnel of parametrium was deroofed and ureter lateralized. Recto vaginal fold of peritoneum was opened and recto vaginal space was created down to levator ani. Uterosacral ligaments were divided lateral to rectum. Lateral bladder pillars were divided. Parametrium was clamped and divided. Vagina was divided with 2- 4 cm cuff. Vault was closed or left open as per the surgeons preference. Bilateral pelvic lymphadenectomy was done clearing all lympho areolar tissue around iliac vessels and obturator fossa. Hemostasis was secured and abdomen was closed in layers.

**Post operative care**

Analgesia was ensured with intra muscular Tramadol and epidural Tramadol /sensorcaine for 2 days. Orals were started after return of bowel sounds (usually 2nd post op day). Patients were mobilized the day after surgery. Urethral catheters were retained till 10th postoperative day and clamped intermittently for bladder sensation from 7th postoperative day. Post void residual urine was assessed on the 10th day. If it was more than 100ml or if the patient developed retention of urine, bladder was recatheterized. Bladder training was done and post void residual urine was assessed again and catheter was removed after 15 days. Sutures were removed on day 10.

**Inoperable patients:**

Patients with tumors that were deemed inoperable because of static disease or progression where radical hysterectomy achieving negative margins would not be possible after neoadjuvant chemotherapy were treated with radical concurrent chemo radiation (cisplatin concurrent with 50 Gy pelvic EBRT and 30 Gy through brachytherapy).

Women with positive nodes, parametrial involvement, cut margins positive after radical hysterectomy and pelvic lymphadenectomy were given additional treatment with chemoradiotherapy (cisplatin concurrent with 50 Gy pelvic EBRT and 30 Gy through brachytherapy). Patients with disease remaining only in the cervix or vagina with negative nodes, no parametrial involvement and all margins negative were treated with vault radiation using low dose rate intra cavitary radiation alone.

**Evaluation of Response**

The response to neoadjuvant chemotherapy was clinically evaluated after the third course and the pathological response was assessed in those patients who underwent surgery.

Responses were registered as follows:

1. Complete response
2. Partial response 1
3. Partial response 2

4. Static disease
5. Progressive disease

***Complete response*** was registered when no clinical or pathological evidence of disease existed. All other cases (persistence or progression) were registered as no complete response.

A complete pathological response to neoadjuvant chemotherapy was registered when no evidence of disease (microscopic or macroscopic) existed.

***Partial response 1*** was registered when there was a ≥50% reduction in the product of the longest perpendicular diameters of the disease and the disease was operable after three cycles of chemotherapy with evidence of gross residual disease

***Partial response 2*** was a partial response with no gross disease residue but microscopic residue only, either in the cervix and/ or the pelvic nodes

***Stable disease*** was <50% reduction or an increase of <25% in the product of the longest perpendicular diameters of the disease making the disease inoperable after 3 cycles of chemotherapy.

***Progressive* disease** with a >25% increase or the appearance of new lesions making the disease inoperable after 3 cycles of chemotherapy.

**Toxicity Assessment**

Toxicity was graded according to Common toxicity criteria for adverse effects of the National Cancer Institute version 4.

**Follow-Up Procedures and Survival:**

Patients were monitored for assessment of disease status 1 month after the end of treatment and every 1 month thereafter for the first year and three monthly thereafter. During each visit complete and pelvic examinations were performed, as well as blood counts, clinical chemistry, ultrasound abdomen and pelvis, vaginal cytology and chest X-rays annually. Computed tomography scans, ultrasound and other studies were carried out when appropriate.

**Statistical Methods**

This was a randomized, single centre study aimed at comparing the activity and toxicity of Fluorouracil +Platin versus Taxol + Platin in the neoadjuvant setting for patients with bulky squamous cell cervical cancer.

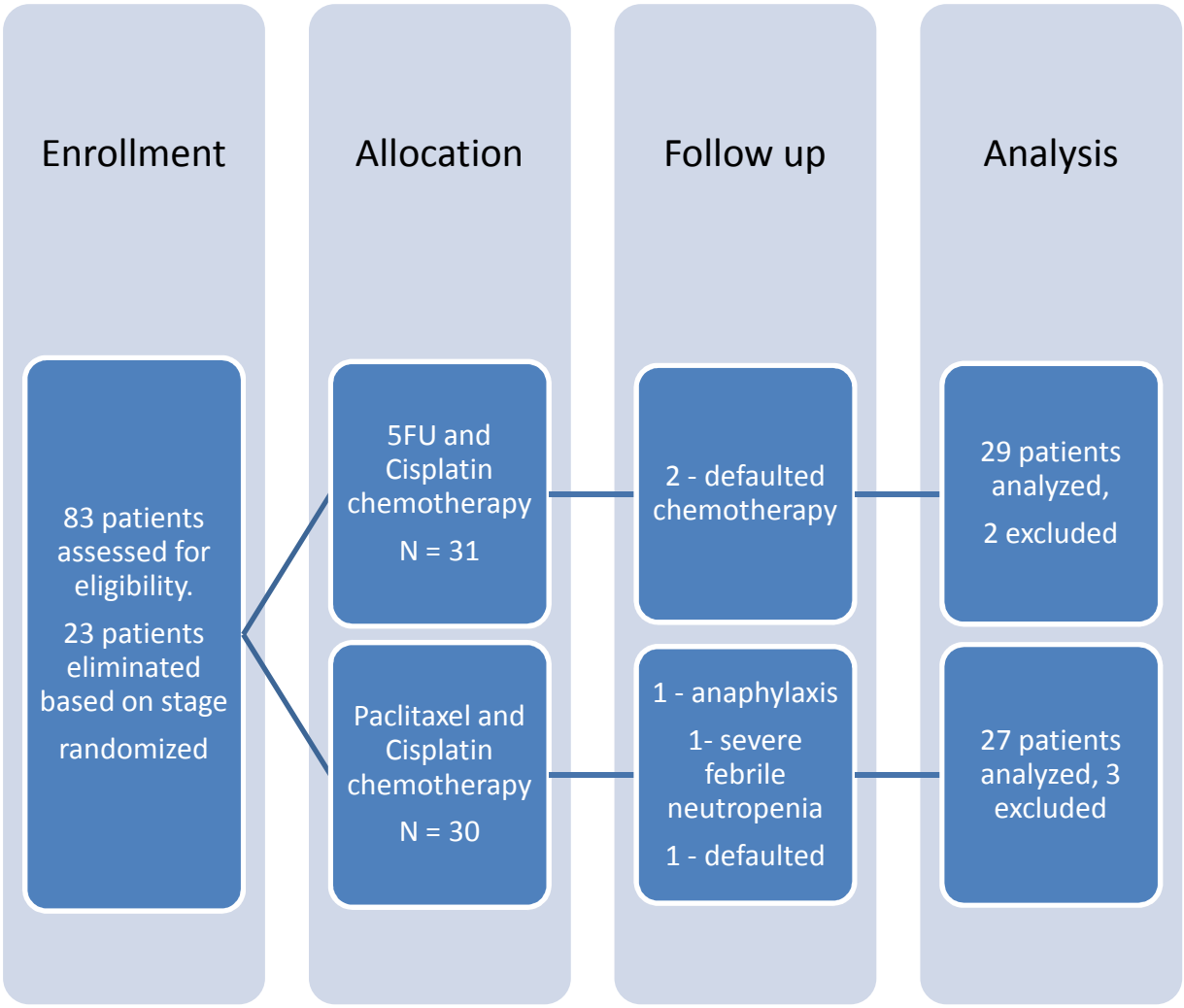
Randomization was done using permutated block method.

The primary efficacy parameter was the response rates. Secondary end points were overall survival and disease-free survival.

**Statistical analysis was performed using SPSS version 16.**

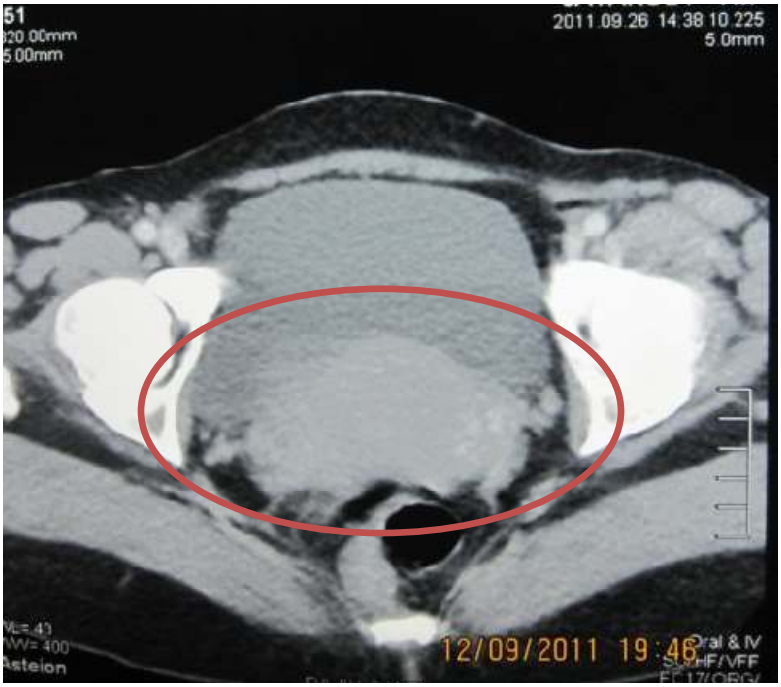
The chi-square and *t*-tests were used when appropriate to compare patient characteristics, responses and toxicity. Influence of clinical, pathological and thereupetic factors on outcome were assessed using a multivariate analysis with a Cox regression model

Consort Diagram



Radiological response

Pre chemo

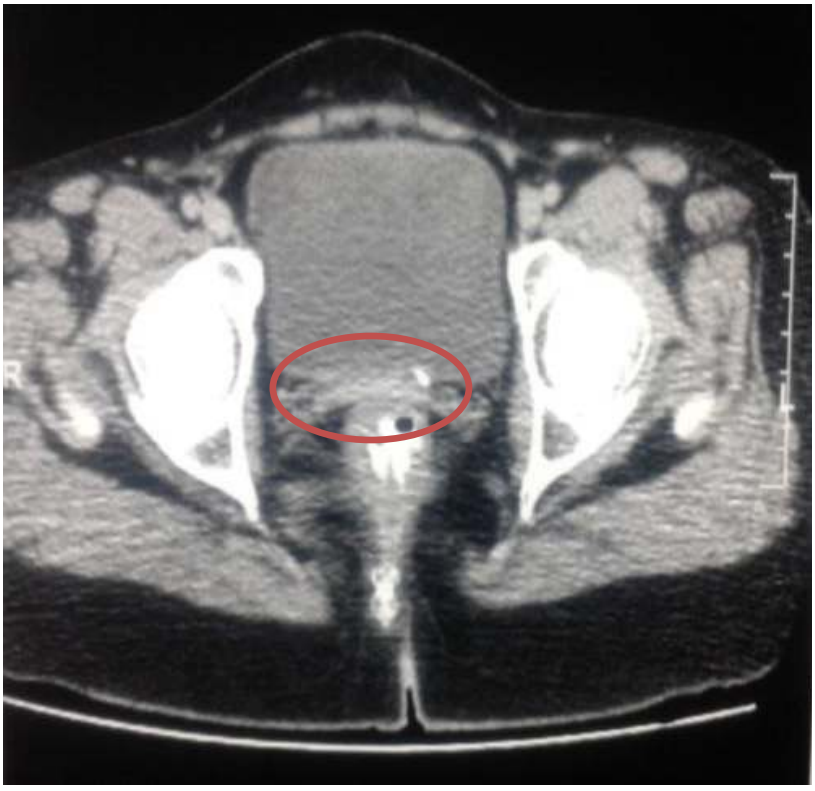



Post chemo

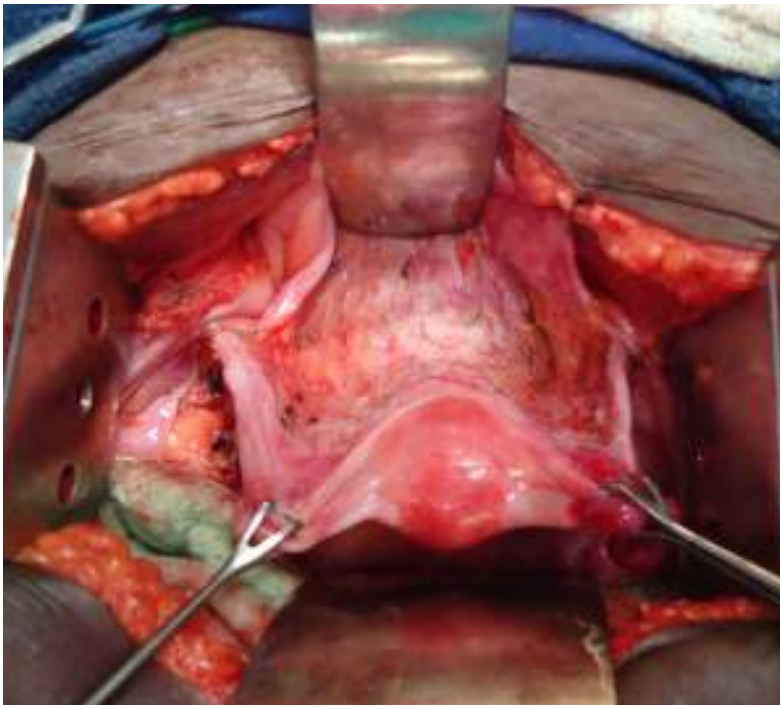
Radiological response

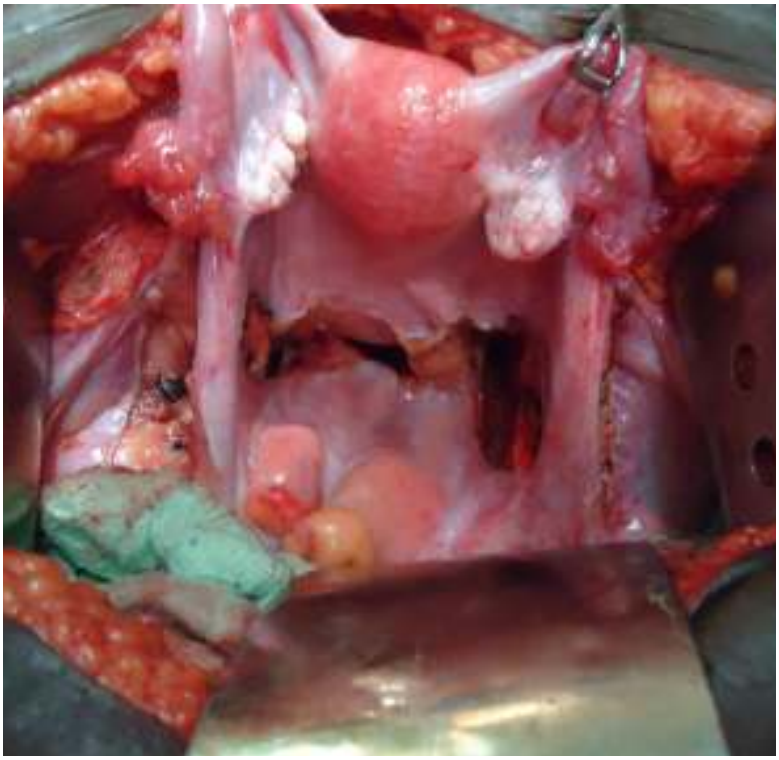
Pre chemo

Post chemo

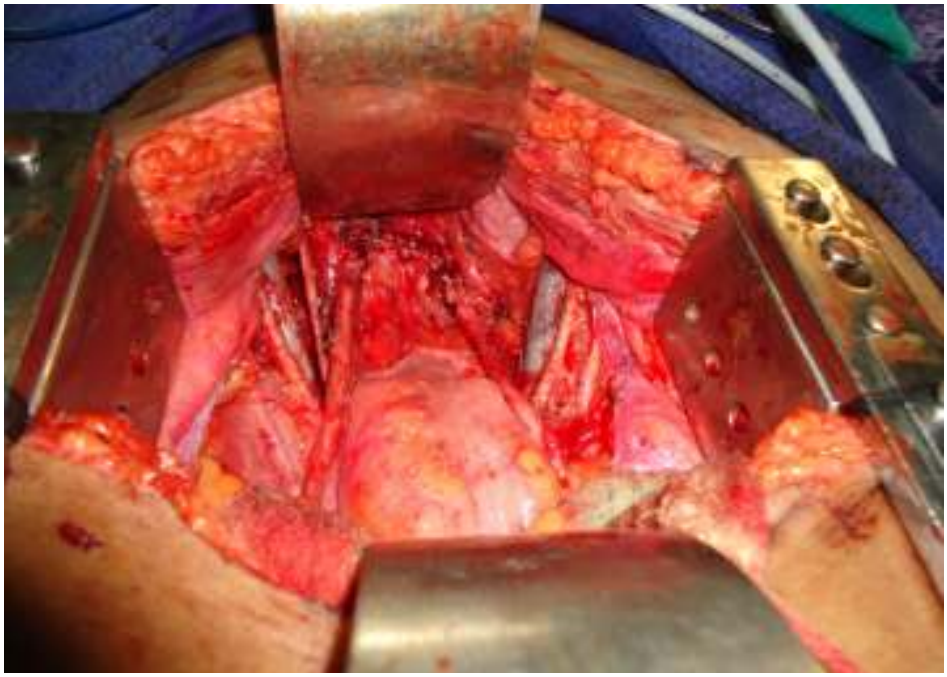


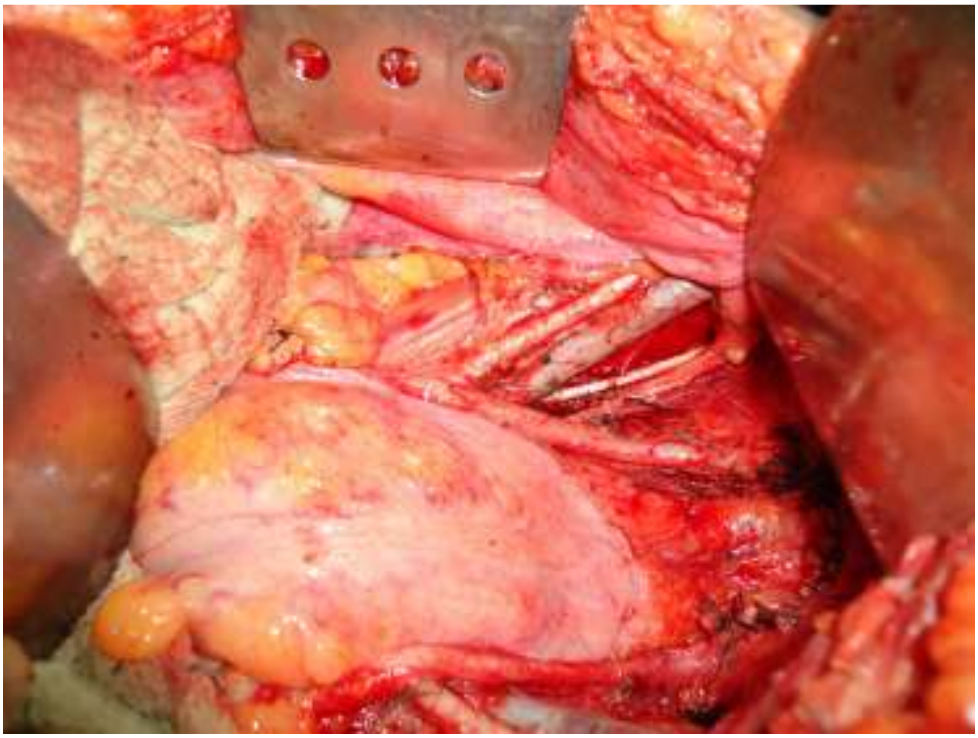
Radical Hysterectomy





Radical Hysterectomy

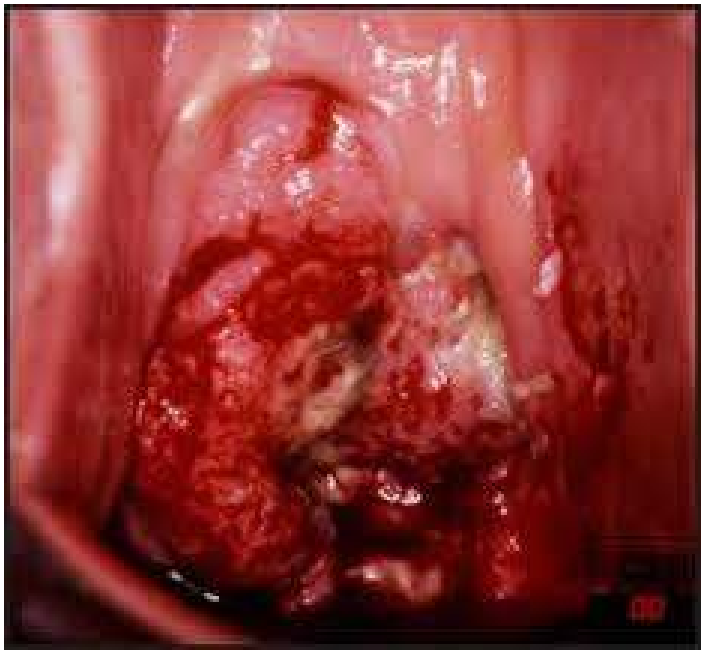




Post operative Specimen


Clinical response

Pre chemo



Post chemo

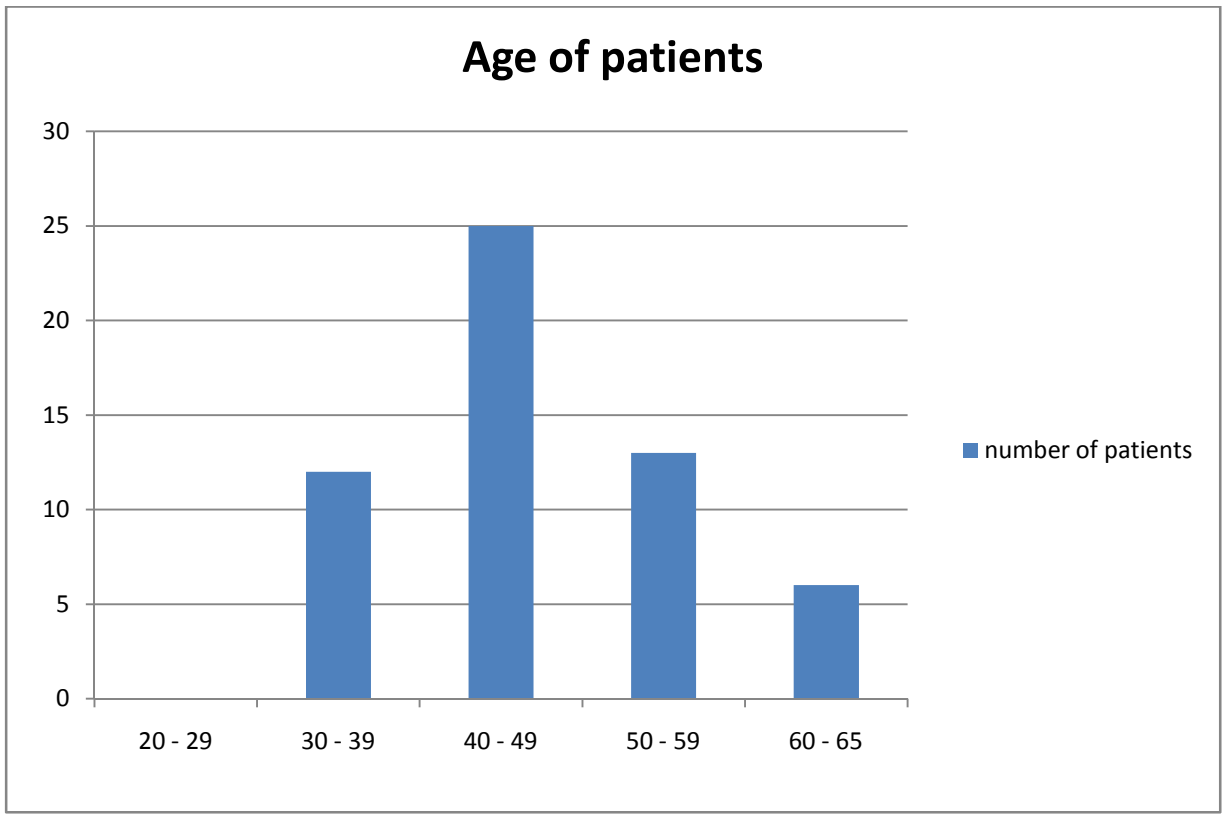
## Case analysis and Results

From September 2010 to February 2013 a total of 61 patients with previously untreated cancer cervix stages IB2, IIA2 and IIB fulfilled the criteria for inclusion in this trial. 5 patients were excluded because one of them developed anaphylaxis to Paclitaxel; another developed severe febrile neutropenia after the first cycle of chemotherapy and the other three patients defaulted during or after the preoperative chemotherapy. Though one of the latter three patients did turn up after one year following three cycles of chemotherapy and she had a complete pathologic response on radical hysterectomy she was not taken up for the analysis because she didn't fit into the time frame of the protocol. The median follow up period was 12months (range 1 – 28 months).

One other patient who had static disease with preoperative chemotherapy was treated with radical chemo radiation and had a residue after chemoradiation. She was surgically salvaged with a total pelvic exenteration and continues to be disease free on follow up.

**Patient demographics**:

A total of 56 patients were enrolled , of whom none were of the 20 – 30 age group,12 were in the 30 – 39 age group, 25 were in the 40 – 49 age group, 13 were in the 50 – 59 age group and 6 were in the 60 – 65 age group. The median age was 47years (range32 -65 years)



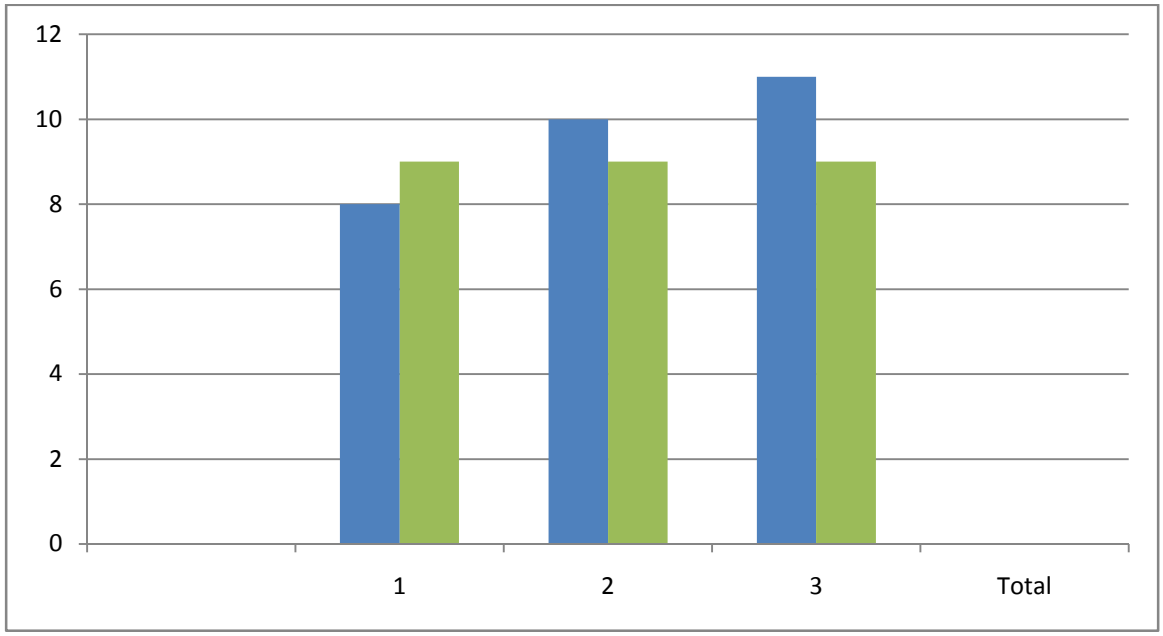

**Tumor characteristics**:

Only Squamous cell carcinomas of the uterine cervix were included in this trial. Of the 56 patients 17 had grade I tumor, 19 had grade II tumor and 20 had grade III tumor.

| Grade of tumor | Chemo Group | | Total |
|---|---|---|---|
| | 5FU + Cisplatin | Paclitaxel + Cisplatin | |
| **1** | 8 | 9 | 17 |
| **2** | 10 | 9 | 19 |
| 3 | 11 | 9 | 20 |

| Grade of tumor | Chemo Group | | Total |
|---|---|---|---|
| | 5FU + Cisplatin | Paclitaxel + Cisplatin | |
| **1** | 8 | 9 | 17 |
| **2** | 10 | 9 | 19 |
| 3 | 11 | 9 | 20 |
| **Total** | **29** | **27** | **56** |

**Grade of tumor in the two chemo groups**



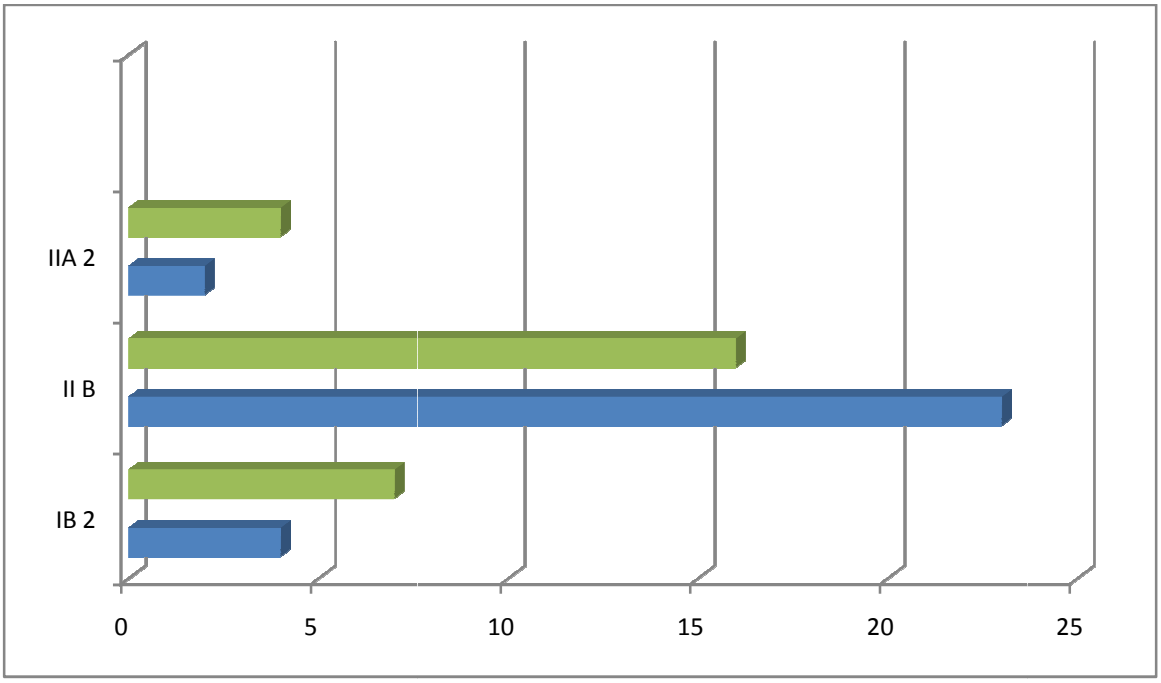

49 had tumor size >4cm and 7 had tumor < 4cm

11 had stage IB2 disease, 6 had stage IIA2 disease, and 39 had stage IIB disease.

| Stage | Chemo_Group | | Total |
|---|---|---|---|
| | 5FU + Cisplatin | Paclitaxel + Cisplatin | |

| | | | |
|---|---|---|---|
| **IB 2** | 4 | 7 | 11 |
| **II B** | 23 | 16 | 39 |
| **IIA 2** | 2 | 4 | 6 |
| **Total** | 29 | 27 | 56 |

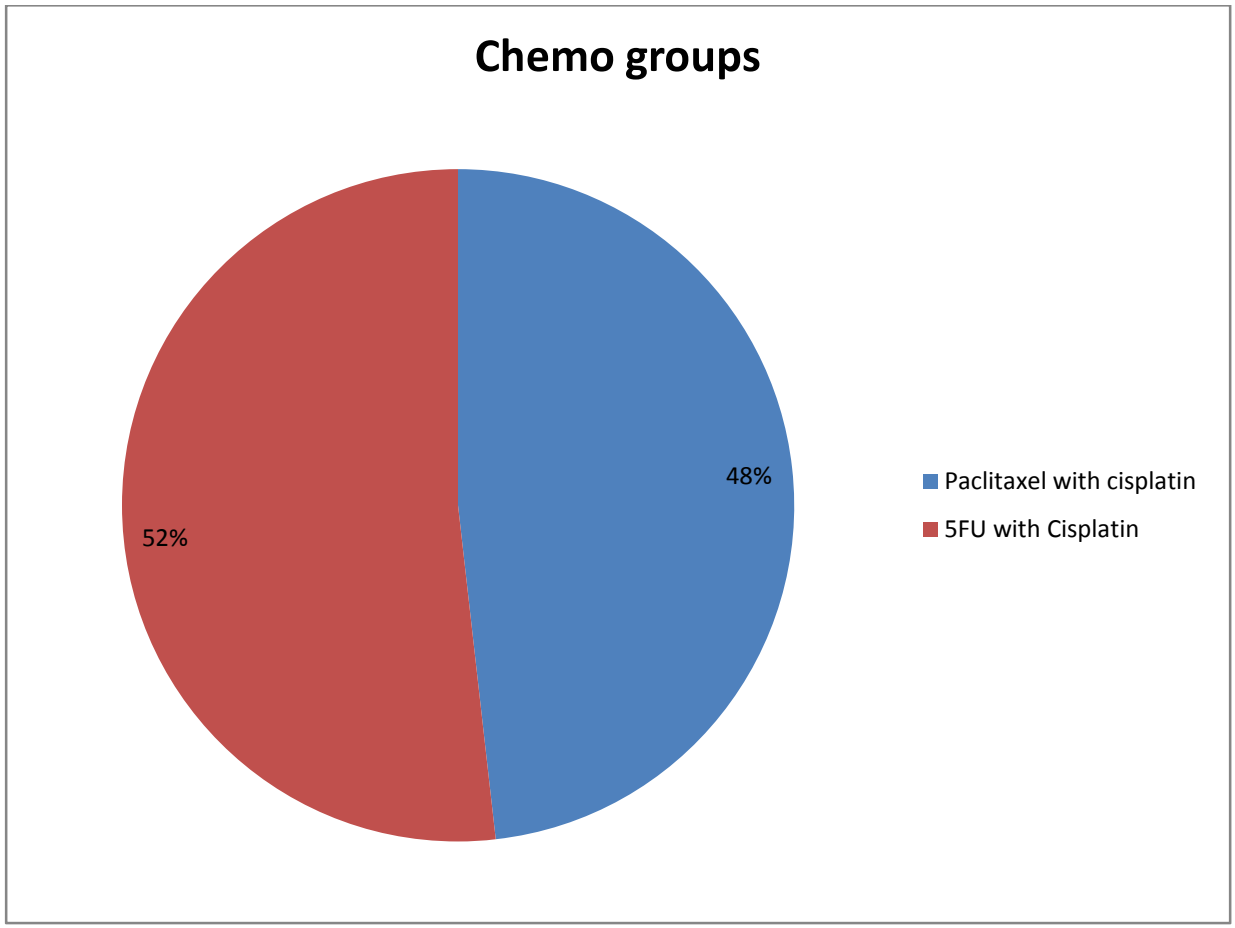
**Stage in the chemo groups**




**Chemotherapy and response**:

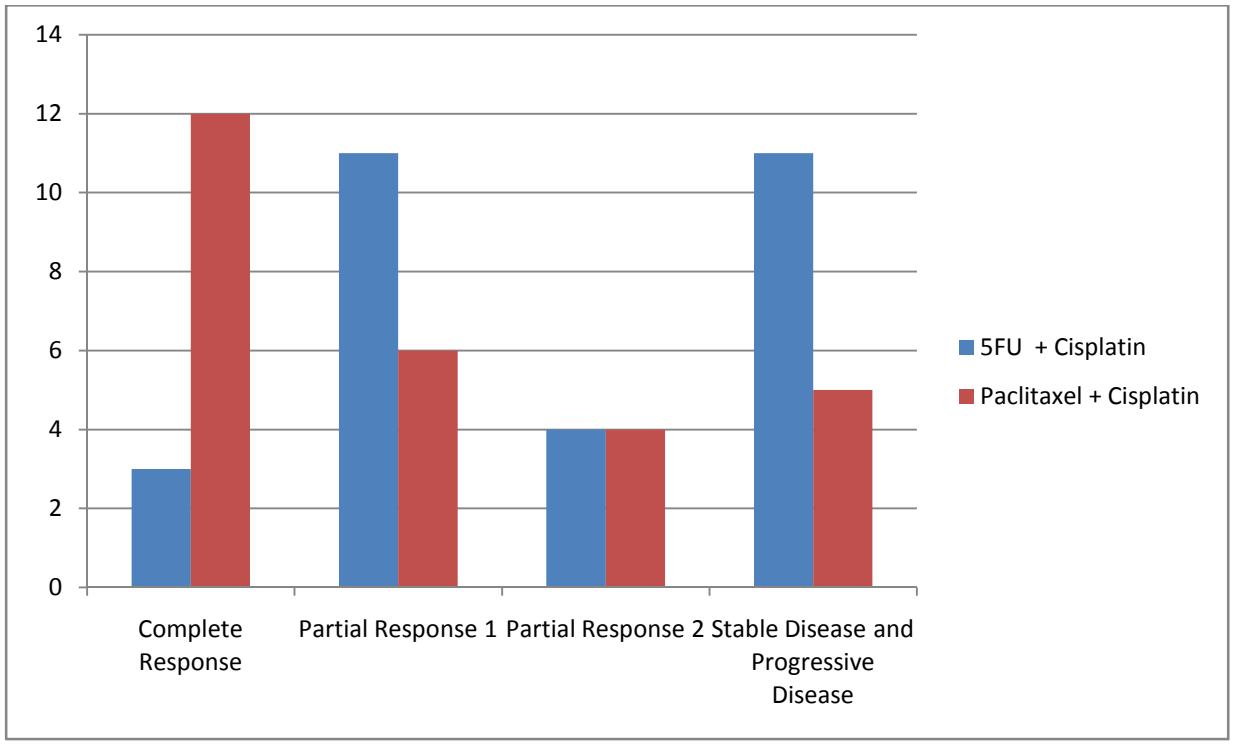
27 Patients received Paclitaxel+ cisplatin chemotherapy and 29 patients received Cisplatin and 5FU chemotherapy.

Of these 40 patients 15 Patients had a complete pathological response. 23 Patients had no macroscopic disease but microscopic residue confined to the cervix alone. 3 Patients had residue in the pelvic nodes. In the Paclitaxel+ cisplatin chemotherapy group 13Patients had a complete pathological response. 8 Patients had no macroscopic disease but microscopic residue confined to the cervix alone. 1 Patients had residue in the pelvic nodes.




In the Cisplatin and 5FU chemotherapy group 1 Patient had a complete pathological response. 15 Patients had no macroscopic disease but microscopic residue confined to the cervix alone. 2 Patients had residue in the pelvic nodes.

| post_chemo_response | Chemo_Group | | Total |
|---|---|---|---|
| | 5FU + Cisplatin | Paclitaxel + Cisplatin | |
| CR | 3 | 12 | 15 |
| PR 1 | 11 | 6 | 17 |
| PR 2 | 4 | 4 | 8 |
| SD + PD | 11 | 5 | 16 |
| Total | 29 | 27 | 56 |




14 Patients received no treatment after the radical hysterectomy, while 22 patients received intracavitary low dose radiation alone and 3 patients received post operative chemoradiation.

| Post operative treatment | Chemo_Group | | Total |
|---|---|---|---|
| | 5FU + Cisplatin | Paclitaxel + Cisplatin | |
| **ICCA only** | 14 | 8 | 22 |
| **Nil** | 1 | 13 | 14 |
| **post op chemo RT** | 2 | 1 | 3 |

Surgical characteristics:

40 patients were taken up for radical hysterectomy with bilateral pelvic lymphadenectomy after completing three cycles of preoperative chemotherapy, 22 patients after the Paclitaxel+ cisplatin chemotherapy and 18 patients after the Cisplatin and 5FU chemotherapy.

The average operating time was 132.25 min (range 90 - mins) with a mean blood loss of 320ml. the average parametrial margin obtained on the right was 22.92mm (range 16 – 28mm) and on the left 22mm (range 14 – 33mm). The nodal yield was an average 7.97(3-12) on the left and 9(4 – 15) on the right. The mean vaginal cuff obtained was 30.375mm (range 22 – 38mm).

| **Operative characteristics** | | | |
|---|---|---|---|
| **Parameter** | **Mean** | **Median** | **Range** |
| **operating time in min** | 132.25 | 130 | 90 - 220 |
| **blood loss in ml** | 319 | 270 | 140 - 1400 |
| **parametrial margin – left in mm** | 21.9 | 22 | 14 - 30 |
| **parametrial margin – right in mm** | 22.8 | 24 | 16 - 28 |
| **nodal yield – left** | 7.92 | 8 | 3 - 12 |
| **nodal yield – right** | 8.92 | 9 | 4 - 15 |
| **Vaginal cuff – in mm** | 30.2 | 30 | 22 - 38 |

**Toxicity of chemotherapy**:

Patients had chemotherapy associated adverse effects.the commonest adverse effect were alopecia and vomiting. 31 patients had alopecia, 14 patients had anorexia, 28 patients had nausea, 31 had vomiting, 6 had allergic reactions, 18 had decreased hemoglobin, 2 had decreased neutrophil counts, no patients had decrease in platelets, 4 had neuropathy and 1 patient had raised creatinine. . Allergic adverse effects were more common in the Paclitaxel and Cisplatin arm compared with the 5 FU and Cisplatin arm. There was no other difference in toxicity profiles among the two groups.

**Operative and post operative complications**:

Post operative bladder morbidity was the commonest complication. 13 Patients had urinary retention, 5 had post operative wound infection, and 3 had operative injury to artery / vein. There was no operative injury to rectum/ bowel / bladder/ ureter in any of the 40 patients who underwent radical hysterectomy with pelvic lymphadenectomy. There was no operative mortality.

**Outcome**

There were 2 deaths among the 56 patients. One patient who had carcinoma cervix stage IIB and completed 3 cycles of chemotherapy with Cisplatin and 5FU followed with a radical hysterectomy and had a partial response (residual macroscopic disease confined to the cervix and vagina with no disease in the pelvic node, parametrium or margins) followed with low dose intracavitary vault irradiation recurred in the pelvis with

inoperable disease after three months. She was treated with chemoradiation but succumbed to the progressive disease 4 months later.

One other patient died of an unrelated cause 8 months after treatment.

With a median follow up of 12 months (range 1 – 29 months) there was only one recurrence among all 56 patients. There were no distant failures.

**Predictive factors of response**

The chemotherapy group was the only significant factor predicting response, and more responses were seen in the Paclitaxel with Cisplatin arm across all groups compared with the 5FU and cisplatin arm.

| Chemo_Group | POST_CHEMO_RESPONSE | | | | Total |
|---|---|---|---|---|---|
| | CR | PR 1 | PR 2 | SD + PD | |
| 5FU + Cisplatin | 3 | 11 | 4 | 11 | 29 |
| Paclitaxel + Cisplatin | 12 | 6 | 4 | 5 | 27 |
| Total | 15 | 17 | 8 | 16 | 56 |

**Chi-Square Test**

| | Value | df | Significance . (2-sided) |
|---|---|---|---|
| Pearson Chi-Square | 9.061 | 3 | .028 |
| N of Valid Cases | 56 | | |

**Predictive factors of cervical residue**

Residue in the cervix after chemotherapy was more common in the 5FU and Cisplatin arm compared with the Paclitaxel and Cisplatin arm. The responses were complete more often in the Paclitaxel and Cisplatin arm

| Chemo_group | No residual tumor | Residual SCC involving cervix and vagina,parametrium free, margins free, nodes ++ | Residual scc in cervix, margins, nodes free | N |
|---|---|---|---|---|
| 5FU + Cisplatin | 2 | 2 | 15 | 19 |
| Paclitaxel + Cisplatin | 13 | 1 | 8 | 22 |
| Total | 14 | 3 | 23 | 40 |

**Chi-Square Test**

| | Value | df | Significance (2-sided) |
|---|---|---|---|
| Pearson Chi-Square | 14.947 | 3 | .002 |
| N of Valid Cases | 40 | | |

## DISCUSSION

Cervical carcinoma remains among the most common and lethal malignancies in women world over [17]. In early stages of the disease, surgery and radiation are equally effective treatment modalities conferring good results [18]; but by themselves, these treatment modalities in locally advanced cases are suboptimal. The most common failures are pelvic with or without systemic relapses.

Neoadjuvant chemotherapy looks to be a good alternative to surgery and irradiation for initial treatment of locally advanced cervical cancer. The potential benefits of this approach are:

i. Reduces the size of tumors
ii. Renders inoperable tumors (international federation of gynecology and obstetrics [FIGO] stages IB2, IIA2, IIB TO IIIB) operable without radiotherapy
iii. Radiotherapy may be kept in reserve as salvage if a pelvic recurrence occurs
iv. Surgery can undo the cross-resistance that occurs between chemotherapy and radiation when they are delivered sequentially
v. It eradicates micrometastases

This aspect of down staging disease without irradiation is attractive and offers a totally new philosophy of treatment for locally advanced cervical cancer.

**Patient characteristics**:

In this study patients in both chemotherapy groups were well matched age wise and there was no significant effect of age on the response rates or the adverse effects encountered. Grade of the tumor and tumor size also did not have a significant role in the responses or the outcomes.

**Chemotherapy and response**:

There was a significantly better response rate with the Paclitaxel and Cisplatin chemotherapy compared with the Cisplatin and 5FU chemotherapy. More responses were complete in the Paclitaxel and Cisplatin chemotherapy arm, and with previous studies indicating that the complete responses translated into better survivals, this may indicate that this combination may be more efficacious than the Cisplatin and 5FU combination.

With the median follow up of 12 months and only one recurrence the disease free survival could not be assessed. Longer follow up of these patients may yield more interesting insights into the benefit of preoperative chemotherapy in avoiding radiation in carcinoma cervix especially in our part of the world with scarce resources where carcinoma cervix is still a rampant problem frequently presenting in bulky or advanced stages.

**Surgical characteristics**:

Radical Hysterectomy and bilateral pelvic lymphadenectomy was done in 40 patients after achieving an optimal response rendering them operable- with supple parametria and non bulky disease with free vaginal margins and the operative characteristics were studied.

The operating times and average blood loss were not significantly increased when compared with radical hysterectomy performed upfront in our institute as quoted in previous studies. Infact with less fibrosis compared with radiotherapy, the tissues were supple and operating times and blood loss was less than when performing radical hysterectomy after radiotherapy. The parametrium obtained, the vaginal cuff and the nodal yield were all comparable with radical hysterectomy done upfront and were not compromised.

**Toxicity of chemotherapy**:

With adequate premedication, toxicity of the preoperative chemotherapy was tolerated well by most patients. Nausea and vomiting were present only in lower grades and no high grade adverse effect requiring intense management was encountered. Allergic adverse effects were more common in the Paclitaxel and Cisplatin arm compared with the 5 FU and Cisplatin arm, possibly due to the Paclitaxel. The other adverse effects were well matched in both groups.

**Operative and post operative complications**:

Operative complications were not significantly increased in the patients who underwent radical hysterectomy after preoperative chemotherapy. No bladder/ ureter/ bowel/ rectal injuries were encounterd in any of the patients. However there was a small increase in injury to arteries or veins, in one case with significant exsanguinations requiring transfusion, but none required reconstruction or bypass (that is grade 2 and less).This may possibly indicate a response of the nodes to chemotherapy with a reaction rendering them adherent to the vasculature leading to injuries. But with adequate surgical expertise in a centre performing large volumes of pelvic surgeries this was not a problem to face at the cost of increased complete responses.

**Outcome**:

Of 56 patients, 40 patients could be taken for surgery after preoperative chemotherapy and of these 40 only 3 required post operative chemo radiotherapy. 14 Patients received no treatment after the radical hysterectomy, while 22 patients received intracavitary low dose radiation. Thus radiotherapy was totally avoided in 14 patients and only small dose of intracavitary radiation was required in 22 patients (a total of 36 of the 56 patients) who would have traditionally been managed with chemoradiation or radiation and surgery. This presents an attractive option in management of carcinoma cervix in resource scarce countries at the same time avoiding the morbidity of radiation in this group of patients.

## CONCLUSION

1. Preoperative chemotherapy in carcinoma cervix is effective in reducing tumor volume and the stage of the disease making bulky stage IB, IIA and IIB disease operable. It may present an attractive option in patients with bulky inoperable tumors of the cervix avoiding radiation and keeping it in reserve for the salvage of recurrences.
2. Paclitaxel with cisplatin yields better response rates (more complete responses) than 5FU and cisplatin and maybe a better drug combination for preoperative chemotherapy in carcinoma cervix.
3. Neoadjuvant chemotherapy with Paclitaxel and cisplatin followed by radical surgery for patients with bulky inoperable cervical Squamous cell carcinoma is a promising mode of treatment that may improve the prognosis. The response rates were good, but longer term follow up is required to assess the benefit on survival and disease free rates. It would be worthwhile to conduct larger-scale trials with a longer follow up for comparison with the results of the chemoradiation therapy study.

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ETHICAL COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE, KILPAUK,
CHENNAI- 10.
Venue: PANAGAL HALL, KMC
Dt: 02.11.2010
CHAIRPERSON
Prof. Dr.V.KANAGASABAI, MD.,
Dean
Govt. Kilpauk Medical College, Chennai-10

Sub: Ethical Committee project work - approved – regarding.

Ref: Lr.No.3944/Audit/E1/09 Dt. 29.10.2010

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With above reference, the Institutional Ethical committee meeting for the following students was conducted at our Institution on 02.11.2010.

| S.NO. | Name | Topic |
|---|---|---|
| 1 | Dr.R.Umadevi, Prof. of Community Medicine, KMC | Training needs assessment survey |
| 2. | Dr.Malini, PG student in O & G, KMC | Association of Uric Acid concentrations with insulin Resistance and Birth weight in Normotensive Pregnant Women . |
| 3. | Dr.M.K.Vedashree, PG student in MD(Pat) | Clinicopathologic study of breast carcinoma with correlation to hormone receptor status & Her 2 neu |
| 4. | Dr.Sujay Sankar, PG student in Mch (Sur ong) | Trial of Neoadjuvant chemotherapy using Paclitaxel and cisplatin or 5- Fluoro uracil and cisplatin followed by radical surgery in patients with bulky squamous cell cervical carcinoma |
| 5. | Dr.P. Kathavel Kumaran, PG student in Mch (Sur ong) | Trivial of sentinel lymph node biopsy (SLNB) using blue dye in oral cancers. |
| 6. | H.Srirupa & V.Sneha Under Graduate | Assessing altered Sleep pattern among Medical Students |

We are glad to inform you that at the Ethical Committee meeting, the documents were discussed and the above short term projects are Ethically approved.

Project 6 students are instructed to get the questionnaire approved by the committee before starting the project.

CHAIRPERSON
For DEAN
Govt. Kilpauk Medical College,
Chennai-10.

To: The Individuals

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Originality | GradeMark | PeerMark

Study of Preoperative Chemotherapy in
BY SUJAY SUSIKAR 18104152 MCH SURGICAL ONCOLOGY

turnitin

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# STUDY OF PREOPERATIVE CHEMOTHERAPY IN CERVICAL CANCERS STAGES IB2, IIA2 AND IIB

DEPARTMENT OF SURGICAL ONCOLOGY

KILPAUK MEDICAL COLLEGE AND

GOVERNMENT ROYAPETTAH HOSPITAL

CHENNAI

*Dissertation submitted in partial fulfillment of*

MCH BRANCH VII (SURGICAL ONCOLOGY) EXAMINATION

AUGUST 2013

29

Match Overview

| | | |
|---|---|---|
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MASTER CHART

| No. | Name | Age | CD Number | alopecia - grade | anorexia | nausea | vomiting | allergy | hemoglobin | neutrophils | platelets | neuropathy | creatinine | renal failure | operative injury to bladder/ ureter | operative injury to rectum/ bowel | operative injury to artery/ vein | post operative wound infection | urinary retention | post op HPE | post op treatment | last follow up in months | recurrence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | G | 38 | 1082/10 | 2 | nil | 1 | 2 | nil | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 28 | |
| 2 | M | 42 | 1121/10 | 2 | nil | 2 | 2 | 2 | nil | nil | nil | nil | nil | nil | nil | nil | 1 | nil | nil | | | 26 | |
| 3 | L | 50 | 1330/10 | 2 | 1 | 1 | 1 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 29 | |
| 4 | M | 45 | 1329/10 | 2 | nil | 2 | 2 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 27 | |
| 5 | V | 37 | 1421/10 | nil | 1 | 2 | 2 | nil | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 7 | + |
| 6 | A | 55 | 1506/10 | nil | 1 | 2 | 1 | nil | 3 | nil | nil | nil | nil | nil | nil | nil | nil | nil | 1 | RCO | ICCA | 22 | |
| 7 | S | 56 | 1547/10 | 2 | nil | nil | 1 | nil | 2 | 1 | nil | 2 | nil | nil | nil | nil | nil | nil | 2 | NR | nil | 20 | |
| 8 | D | 38 | 30/11 | 2 | nil | 2 | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 2 | RCO | ICCA | 18 | |
| 9 | Y | 38 | 198/11 | nil | 2 | 2 | 2 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 16 | |
| 10 | V | 66 | 295/11 | 1 | nil | nil | nil | nil | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | 1 | RCO | ICCA | 16 | |
| 11 | K | 34 | 297/11 | nil | nil | 1 | nil | nil | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 14 | |
| 12 | P | 35 | 311/11 | nil | 1 | 2 | 2 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 15 | |
| 13 | S | 40 | 370/11 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | NR | nil | 18 | |
| 14 | D | 36 | 406/11 | nil | 1 | 1 | 2 | nil | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 14 | |
| 15 | S | 50 | 432/11 | 1 | nil | 1 | 1 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | 1 | RCO | ICCA | 19 | |
| 16 | V | 50 | 531/11 | 2 | nil | nil | nil | nil | nil | nil | nil | 1 | nil | nil | nil | nil | 1 | nil | nil | RCO | ICCA | 11 | |
| 17 | T | 40 | 541/11 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 17 | |
| 18 | D | 47 | 731/11 | 2 | nil | nil | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | NR | nil | 18 | |
| 19 | S | 47 | 854/11 | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 16 | |
| 20 | L | 55 | 932/11 | nil | 1 | 1 | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 14 | |
| 21 | S | 65 | 972/11 | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 2 | nil | RNP | CRT | 15 | |
| 22 | S | 32 | 1000/11 | 2 | 1 | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 3 | 2 | NR | nil | 15 | |
| 23 | M | 48 | 1033/11 | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 14 | |
| 24 | L | 37 | 1066/11 | 2 | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 12 | |
| 25 | B | 45 | 1178/11 | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RNP | CRT | 15 | |

MASTER CHART

| | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 | M | 40 | 1177/11 | 2 | nil | 2 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | NR | nil | 13 | |
| 27 | S | 50 | 1162/11 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 2 | | | 12 | |
| 28 | M | 50 | 1182/11 | 2 | nil | nil | nil | nil | nil | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 12 | |
| 29 | S | 48 | 1195/11 | nil | nil | nil | nil | nil | nil | nil | nil | 2 | nil | nil | nil | nil | nil | nil | nil | NR | nil | 11 | |
| 30 | N | 52 | 1308/11 | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 11 | |
| 31 | M | 52 | 1317/11 | 1 | 1 | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 10 | |
| 32 | K | 38 | 1347/11 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 1 | 1 | RCO | ICCA | 10 | |
| 33 | A | 41 | 1348/11 | 1 | Nn | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 13 | |
| 34 | M | 40 | 1386/11 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | NR | nil | 12 | |
| 35 | M | 63 | 1376/11 | 2 | nil | nil | 1 | nil | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 11 | |
| 36 | V | 61 | 34/12 | nil | 1 | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 2 | 1 | RCO | ICCA | 12 | |
| 37 | K | 48 | 266/12 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 9 | |
| 38 | V | 40 | 287/12 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | NR | nil | 7 | |
| 39 | P | 58 | 313/12 | 2 | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 1 | NR | nil | 7 | |
| 40 | V | 48 | 331/12 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | NR | nil | 9 | |
| 41 | P | 42 | 432/12 | 2 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 8 | |
| 42 | L | 45 | 525/12 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 7 | |
| 43 | L | 55 | 639/12 | 2 | nil | 1 | 1 | nil | nil | nil | nil | nil | 1 | nil | nil | nil | nil | nil | 1 | | | 7 | |
| 44 | S | 55 | 739/12 | 2 | nil | nil | nil | nil | 1 | nil | nil | 2 | nil | nil | nil | nil | nil | nil | nil | NR | nil | 4 | |
| 45 | T | 43 | 763/12 | 2 | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | NR | nil | 4 | |
| 46 | V | 48 | 854/12 | 2 | nil | nil | nil | nil | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | RNP | CRT | 3 | |
| 47 | V | 36 | 873/12 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | RCO | ICCA | 3 | |
| 48 | M | 36 | 1016/12 | nil | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | 2 | 3 | nil | NR | nil | 2 | |
| 49 | A | 47 | 1050/12 | 2 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 4 | |
| 50 | J | 48 | 1076/12 | nil | 1 | 3 | 2 | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | | | 4 | |
| 51 | S | 46 | 1077/12 | | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 3 | |
| 52 | A | 40 | 1081/12 | 2 | nil | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 3 | |
| 53 | M | 60 | 1085/12 | nil | nil | 1 | 2 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | 2 | NR | nil | 2 | |
| 54 | M | 62 | 1095/12 | 1 | trade | nil | 1 | 1 | nil | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 3 | |
| 55 | A | 42 | 2008/12 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 1 | |
| 56 | L | 52 | 2014/12 | nil | nil | 1 | 1 | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | nil | | | 1 | |